

Australasian Paediatric Endocrine Group



Australian
Diabetes
Society

National Evidence-Based Clinical Care Guidelines for Type 1 Diabetes in Children, Adolescents and Adults

© Commonwealth of Australia 2011

Printed document

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Communications Branch, Department of Health and Ageing, GPO Box 9848, Canberra ACT 2601, or via e-mail to copyright@health.gov.au.

Electronic document

This work is copyright. You may download, display, print and reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Communications Branch, Department of Health and Ageing, GPO Box 9848, Canberra ACT 2601, or via e-mail to copyright@health.gov.au.

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (up to December 2010). The guidelines are not meant to be proscriptive. The relevance and appropriateness of the information and recommendations in this document depend on individual circumstances. Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

Copies of this guideline can be downloaded from the websites of the Australasian Paediatric Endocrine Group [APEG] (www.apeg.org.au) and the Australian Diabetes Society [ADS] (www.diabetessociety.com.au).

Funding

The Australasian Paediatric Endocrine Group and the Australian Diabetes Society acknowledge the financial assistance provided by the Australian Government Department of Health and Ageing.

Published: 14 Nov 2011

ISBN Online: 978-0-9872203-0-1

Suggested citation

Craig ME, Twigg SM, Donaghue KC, Cheung NW, Cameron FJ, Conn J, Jenkins AJ, Silink M, for the Australian Type 1 Diabetes Guidelines Expert Advisory Group. *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults*, Australian Government Department of Health and Ageing, Canberra 2011.

Co-chairs

Associate Professor Maria Craig (APEG), Professor Stephen Twigg (ADS).

Executive

Professor Fergus Cameron (APEG), Associate Professor N Wah Cheung (ADS), Dr Jennifer Conn (ADS), Professor Kim Donaghue (APEG), Associate Professor Alicia Jenkins (ADS), Professor Martin Silink (APEG).

Expert Advisory Group

Dr Linda Beeney (ADS), Dr Neale Cohen (ADS), Professor Stephen Colagiuri (ADS), Dr Louise Conwell (APEG), Professor Jenny Couper (APEG), Ms Nuala Harkin (Australian Diabetes Educators Association [ADEA]), Professor Mark Harris (Royal Australian College of General Practitioners [RACGP]), Ms Heather Hart (ADEA), Dr Jane Holmes-Walker (ADS), Dr Craig Jefferies (APEG), Dr Tony Lafferty (APEG), Ms Eunice Lang (APEG), Clinical Professor Tim Jones (APEG), Associate Professor Maarten Kamp (ADS), Professor Richard Maclsaac (ADS), Ms Kate Marsh (ADS, Dietitians Association of Australia [DAA]), Dr Alison Nankervis (Australasian Diabetes in Pregnancy Society [ADIPS], ADS), Dr Mark Pascoe (APEG), Associate Professor Christine Rodda (APEG), Dr Tony Russell (ADS), Ms Carmel Smart (APEG, DAA), Dr Jennifer Wong (ADS), Dr Helen Woodhead (APEG), Associate Professor Sophia Zoungas (ADS), Ms Renza Scibilia (Diabetes Australia Ltd [DA]) and Ms Chanelle Stowers (Juvenile Diabetes Research Foundation [JDRF]).

Support staff

Expert methodological consultants: Dr Lisa Elliot and Dr Sarah Norris (Health Technology Analysts); Project officers: Dr Kerri-Ann Chow, Mr Daniel Davies, Ms Maria Gomez, Ms Helen Phelan; Medical writing: Dr Hilary Cadman; Secretarial and executive support staff: Ms Suzie Neylon (ADS) and Ms Lyndell Wills (APEG).

Contact

APEG Secretariat, PO Box 180, Morisset NSW 2264

Email: apeg@willorganise.com.au or Tel: 02 4973 6573, or

ADS Secretariat, 145 Macquarie Street, Sydney NSW 2000

Email: suzie@diabetessociety.com.au Tel: 02 9256 5462

Publication approval



Australian Government

National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 16 August 2011, *under Section 14A of the National Health and Medical Research Council Act 1992*. In approving these guidelines, the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Endorsements:

The guidelines have been endorsed by the following organisations:

Australasian Diabetes in Pregnancy Society (ADIPS)

Australian Diabetes Educators Association (ADEA)

Australian Paediatric Society (APS)

Diabetes Australia (DA)

Pharmacy Guild of Australia

Type 1 Diabetes Network (T1DN)

JDRF is pleased to offer their congratulations to the Government, the NHMRC and the authors on their efforts in researching and compiling the first comprehensive evidence-based guidelines for the treatment and care of all individuals with type 1 diabetes in Australia. This initiative is supported by JDRF but the content may not reflect the views of all members of the Foundation.

Contents

Preface	1
Executive summary.....	2
1 Introduction	15
1.1 Development of the guidelines.....	15
1.2 Purpose, healthcare settings and target audience	16
1.3 Population groups.....	17
1.4 Governance structure	17
1.5 Structure of the document and related materials.....	17
1.5.1 The document.....	17
1.5.2 Related materials.....	18
2 Methods.....	19
2.1 Clinical research questions – development and details	19
2.2 Review and research.....	19
2.2.1 Systematic review process.....	19
2.2.2 Study Assessment Criteria	20
2.2.3 Background material.....	22
2.3 Development of evidence statements, recommendations and practice points	24
2.4 Description of public consultation.....	26
3 Natural history and prevention	27
3.1 Introduction	27
3.2 Epidemiology	27
3.3 Preclinical diabetes	28
3.4 Interventions to delay or prevent the onset of type 1 diabetes	28
3.4.1 Insulin.....	29
3.4.2 Nicotinamide.....	29
3.4.3 Day-care exposure	29
3.4.4 Vitamin D	29
3.4.5 Summary.....	30
3.5 Presentation of diabetes.....	31
3.6 Acute complications	31
3.6.1 Reduced hypoglycaemia awareness.....	32

3.6.2	Diabetic ketoacidosis	32
3.7	Chronic complications	32
3.7.1	Microvascular complications	32
3.7.2	Macrovascular complications	33
3.7.3	Weight.....	33
3.8	Prevention of complications.....	33
4	Impact of type 1 diabetes on the individual and society	34
4.1	Psychological health in type 1 diabetes.....	34
4.1.1	Psychological distress	34
4.1.2	Psychological adjustment, wellbeing and functioning	34
4.1.3	Psychiatric disorders	35
4.1.4	Summary	37
4.2	What is the impact of type 1 diabetes on cognitive performance?	38
4.2.1	Children.....	39
4.2.2	Adults	39
4.2.3	Summary	40
4.3	The impact of type 1 diabetes on growth and physical development	41
4.3.1	Summary	42
4.4	Urban versus rural care of type 1 diabetes in Australia	42
4.4.1	Summary	43
4.5	The cost burden of type 1 diabetes to individuals and society	43
5	Role of major trials in advancing clinical care in blood glucose management	46
5.1	Introduction	46
5.1.1	Diabetes Control and Complications Trial	46
5.1.2	Epidemiology of Diabetes Interventions and Complications study	49
5.2	Across the lifespan.....	51
5.3	Metabolic control matters – putting glycaemic control into context	51
5.4	Glycaemic target setting	52
5.4.1	HbA1c.....	52
5.4.2	Blood glucose targets	52
5.5	Relationship between HbA1c and blood glucose level.....	53
5.6	Measurement of HbA1c.....	53
6	Blood glucose monitoring	54
6.1	Continuous real time monitoring vs standard management	55

6.2	Continuous retrospective monitoring vs standard management	58
6.3	Cost and cost-effectiveness of real-time and retrospective monitoring versus standard management	59
7	Insulin and pharmacological therapies	60
7.1	Insulin analogues versus human insulin	60
7.1.1	Comparison of insulin analogues and human insulin in reducing hypoglycaemia and HbA _{1c}	60
7.1.2	Comparisons of insulin analogues	62
7.1.3	Cost-effectiveness studies	62
7.2	Continuous subcutaneous insulin infusion versus multiple daily injections.....	64
7.2.1	CSII versus MDI	64
7.2.2	Sensor augments CSII versus MDI	66
7.2.3	Cost-effectiveness studies	67
7.3	Metformin as an adjunct to insulin.....	68
8	Health-care delivery	70
8.1	Ambulatory care	71
8.1.1	At diabetes onset.....	71
8.1.2	Type of educational needs at diabetes diagnosis in adults	72
8.1.3	After diabetes onset	72
8.2	Telemedicine.....	74
9	Education and psychological support.....	75
9.1	Psychological screening tools	75
9.2	Education and psychological support programs.....	77
9.2.1	Metabolic outcomes	78
9.2.2	Psychological outcomes.....	79
9.2.3	Summary.....	80
9.2.4	Cost and cost effectiveness of different education programs	81
10	Nutrition	83
10.1	Carbohydrate quantification.....	84
10.2	Glycaemic index.....	85
10.3	Protein	87
10.4	Fat	88

11	Exercise	90
11.1	Modification of Insulin type, dose and mode of delivery with exercise	90
11.2	General principles in initial exercise planning	91
11.2.1	Carbohydrate requirement.....	91
11.2.2	Insulin therapy	91
11.2.3	Glycaemic control	92
11.3	Fine tuning an initial exercise regimen through monitoring	93
11.3.1	Sprinting.....	93
11.3.2	Preventing nocturnal hypoglycaemia	93
11.3.3	Hypoglycaemia and recreational sport.....	94
11.3.4	Preventing hypoglycaemia in children.....	94
11.3.5	Preventing hypoglycaemia in adolescents and adults when exercise is combined with alcohol.....	94
12	Complementary and alternative medicines	95
12.1	Effectiveness, cost and cost effectiveness of complementary therapies and alternative medicines	95
12.1.1	Effectiveness of complementary and alternative medicines	95
12.1.2	Cost-effectiveness studies	96
12.1.3	Summary.....	96
13	Maternal pregnancy and fetal outcomes	98
13.1	Effectiveness of preconception care	98
13.2	Effectiveness of blood glucose control	100
13.3	Effectiveness of insulin pumps and CGMS during pregnancy	102
13.3.1	Effect of CSII in pregnancy on achieving blood glucose targets and improving maternal and fetal outcomes?.....	102
13.3.2	Effect of CGMS, real-time blood glucose monitoring and sensor-augmented CSII therapy in pregnancy on achieving blood glucose targets and improving maternal and fetal outcomes?	102
13.4	Diabetes complications monitoring during pregnancy.....	102
13.4.1	Summary.....	103
14	Contraception	104
14.1	Introduction	104
14.2	Summary.....	105

15	Transition of care from paediatric to adult health services	106
15.1	Essential elements in transitional care models from adolescence to adulthood.....	106
15.2	Adult diabetes health service	107
15.3	The role of the general practitioner	108
15.4	Summary	109
16	Hypoglycaemia.....	110
16.1	Predictive factors for severe hypoglycaemia.....	110
16.1.1	Predictors of severe hypoglycaemia.....	111
16.1.2	The effect of intensive diabetes management on the incidence of severe hypoglycaemia.....	112
16.2	Acute effects of severe hypoglycaemia	114
16.3	Prevention of severe hypoglycaemia.....	116
16.4	Efficacy and safety of hypoglycaemia treatments.....	118
16.4.1	Summary.....	121
17	Acute complications – diabetic ketoacidosis and sick-day management	123
17.1	Ketone monitoring.....	123
17.2	Sick-day management.....	125
17.2.1	Practice principles for sick-day management.....	125
17.3	Diabetic ketoacidosis	128
17.3.1	Background	128
17.3.2	Definition of diabetic ketoacidosis	128
17.3.3	Management	129
17.3.4	Summary.....	134
18	Microvascular and macrovascular complications	136
18.1	Effect of intensive glycaemic management on complications	136
18.1.1	Microvascular complications	136
18.1.2	Macrovascular complications	137
18.1.3	Glycaemic control	137
18.1.4	Adverse events	138
18.1.5	Cost effectiveness.....	138
18.1.6	Summary.....	138
18.2	Effectiveness of antihypertensive agents at controlling blood pressure and reducing complications.....	139
18.2.1	Blood pressure control	140
18.2.2	Effectiveness of antihypertensive agents at reducing complications.....	141

18.3	Effectiveness of statin therapy in reducing complications	143
18.4	Cost and cost effectiveness of antihypertensive agents and statins.....	145
18.5	Predictive ability of the Framingham multiple cardiovascular disease risk factor equation in type 1 diabetes?	146
18.6	Frequency of screening for complications.....	146
18.6.1	Mortality rates	147
18.6.2	Value of screening	148
18.6.3	Screening methods	148
18.6.4	Current recommendations for screening	148
18.6.5	Emerging screening technologies	149
18.6.6	Individualised follow-up	150
18.6.7	Other complications	150
19	Foot ulcers and Charcot’s arthropathy	151
19.1	Introduction	151
19.2	Foot complications in young people with type 1 diabetes.....	151
19.3	Foot complications in adults with type 1 diabetes.....	152
19.4	Screening for foot complications in type 1 diabetes	153
19.5	Summary.....	154
20	Other complications and associated conditions	156
20.1	Coeliac disease.....	156
20.1.1	Epidemiology	156
20.1.2	Screening	156
20.1.3	Management	157
20.2	Thyroid disease	158
20.2.1	Epidemiology	158
20.2.2	Clinical features	159
20.2.3	Screening and investigation.....	159
20.2.4	Management	160
21	Future research	162
21.1	Evidence gaps and areas of future research.....	162
21.1.1	Natural history of type 1 diabetes	162
21.1.2	Characteristics of type 1 diabetes	162
21.1.3	Blood glucose monitoring.....	162
21.1.4	Insulin and pharmacological therapies.....	163
21.1.5	Health care delivery	163
21.1.6	Education and psychological support.....	164
21.1.7	Complementary and alternative medicines	164
21.1.8	Maternal pregnancy and fetal outcomes	164

21.1.9	Contraception	165
21.1.10	Acute effects of hypoglycaemia and hyperglycaemia	165
21.1.11	Sick day management and diabetic ketoacidosis	165
21.1.12	Diabetes complications.....	166
21.2	Topics for future consideration	166
21.2.1	Screening for type 1 diabetes	166
21.2.2	Experimental therapies aimed at curing type 1 diabetes.....	166
21.2.3	Maternal pregnancy and fetal outcomes	167
21.2.4	Transition care	167
21.2.5	Reduced hypoglycaemia unawareness.....	167
21.2.6	Complications	167
21.2.7	Foot care	167
22	Implementing, evaluating and maintaining the guidelines.....	168
22.1	Guidelines dissemination.....	168
22.2	Guidelines effectiveness assessment	169
22.3	Guidelines review and updating	169
	Appendix A: Governance	170
	Appendix B: Process report.....	175
	Appendix C: Evidence matrixes	178
	Appendix D: Other resources	218
	Abbreviations and acronyms	220
	References.....	229

Preface

Type 1 diabetes is an increasingly common condition in Australia. Currently, type 1 diabetes is incurable and there is no known way to prevent it. The condition most commonly develops during childhood and adolescence, but can have its onset at any time in life. Following diagnosis, the demands in managing type 1 diabetes have a major effect on the individual's lifestyle in the short and long term, due to the burden of monitoring the disease, taking insulin safely and controlling blood glucose. As the years proceed, especially during adolescence and into adulthood, diabetes end-organ complications become increasingly common in a person with type 1 diabetes, such complications require specific care. Moreover, pregnancy in women with type 1 diabetes demands careful preconception planning, and management throughout gestation. In essence, type 1 diabetes affects nearly every aspect of life for the person with the condition and for their family.

The management of an individual with type 1 diabetes requires a multidisciplinary health-care network delivering integrated clinical care, using a complex array of health-care tools. Through advances in therapy and technology, the quality of life, morbidity and mortality outcomes in people with type 1 diabetes continue to improve in countries with a well-developed health-care system, such as Australia. Demonstrable progress has been made in recent decades and continues to be made, through personalised intensive patient education and self-care, application of new medicines and technologies, and targeted psychosocial support of the person with type 1 diabetes.

This is the first Australian evidence-based guideline for type 1 diabetes that addresses clinical care across the lifespan. Through the collaborative efforts of the Australasian Paediatric Endocrine Group and the Australian Diabetes Society, on behalf of the Australian Government Department of Health and Ageing, this guideline for health-care professionals and consumers addresses key aspects of clinical care for people with type 1 diabetes. The guideline updates the *Clinical practice guidelines: Type 1 diabetes in children and adolescents* (APEG 2005), and extends the scope of that document to address the needs of adults with type 1 diabetes, including pregnancy.

This national evidence-based guideline provides a comprehensive resource for the health-care professional team in the modern clinical care of people with type 1 diabetes in Australia. It should be used in the context of the health-care needs and circumstance of each individual with diabetes.

Associate Professor Maria Craig

Professor Stephen Twigg

Co-chair (APEG)

Co-chair (ADS)

Executive summary

The *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults* is the first national evidence-based clinical care guideline for type 1 diabetes across the lifespan. This document was developed by an Expert Advisory Group (EAG) representing specialist societies and organisations, with the active participation of consumer groups and the community.

This Executive summary includes:

- a summary of the recommendations that were developed by the EAG, based on evidence from a systematic review of the relevant question; each recommendation is numbered to be consistent with to the chapter to which it pertains
- a summary of the practice points that were developed by the EAG through consensus decision-making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations but clinicians require guidance to ensure good clinical practice; as with the recommendations, each practice point is numbered to be consistent with the chapter to which it pertains.

Details of the systematic review used in the development of these guidelines are given in the technical report that accompanies this document.

Materials relevant to health professionals and consumers will be developed to accompany these guidelines; these materials will be available online and in print.

Summary of Evidence, Recommendations and Practice Points

Chapter 3. Natural History and Prevention of type 1 diabetes

Question 3.1	
What interventions delay or prevent the onset of type 1 diabetes?	
Recommendation	
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).
Practice point	
PP3.1	Interventions aimed at delaying or preventing the onset of type 1 diabetes should only be used in a research setting.

Chapter 4. Impact of type 1 diabetes on the individual and society

Question 4.1	
Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?	
Recommendation	
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).
Practice points	
PP4.1.1	Consider the co-occurrence of psychological disorders, including clinical and subthreshold eating disorders, when assessing people with type 1 diabetes and suboptimal glycaemic control, insulin omission, disordered eating behaviours, unexplained weight loss or recurrent admissions for diabetic ketoacidosis (DKA).
PP4.1.2	In young people with diabetes, psychological disorders are relatively common compared with prevalence rates for end-organ complications.
PP4.1.3	The diabetes team should assess family functioning (including parental psychopathology) and diabetes-related functioning, including communication, parental involvement and support, roles and responsibilities for self-care behaviours.
PP4.1.4	Validated screening tools for psychological disorders in type 1 diabetes are available.
Question 4.2	
What is the impact of type 1 diabetes on cognitive performance?	
Recommendation	
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).
Practice points	
PP4.2.1	It is important to monitor the school performance of children who developed diabetes before age 5–7 years, and those with a history of significant hypoglycaemic episodes or chronic poor blood glucose control.
PP4.2.2	Early age of onset of type 1 diabetes is associated with a minor but statistically significant reduction in IQ. Therefore, children experiencing significant learning difficulties should be referred for psycho-educational or neuropsychological evaluation. If learning disabilities are present, alternative causes should be sought and remedial interventions to address specific deficits implemented.

Chapter 6. Blood glucose monitoring

Question 6.1	
Does real-time continuous glucose monitoring (CGM) versus standard management improve HbA _{1c} , minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Recommendation	
R6.1	Real-time CGM may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).
Practice points	
PP6.1.1	Real-time CGM could be considered for use by specialist units, in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. In these situations, use of a hypoglycaemia alarm in a real-time monitoring system may help to treat hypoglycaemia in a timely manner and prevent severe episodes of hypoglycaemia.
PP6.1.2	When combined with CSII therapy, evidence from sensor-augmented CSII studies supports use of real-time CGM to improve HbA _{1c} when they are used at least 70% of the time.
PP6.1.3	It is essential that individuals using these real-time monitoring systems be provided with education in the correct use of the real-time monitoring device and the correct interpretation of results.
PP6.1.4	Real-time CGM systems are not currently reimbursed by the NDSS or health insurance funds. Given current cost constraints, they are most likely to be useful over short periods of time, to aid profile setting and trouble shooting in glycaemic control.
Question 6.2	
Does CGM (retrospective systems) versus standard management improve HbA _{1c} , minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Recommendation	
R6.2	Retrospective CGM systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for children and adolescents (Grade C).
Practice points	
PP6.2.1	Retrospective CGM systems could be considered for use by specialist units, in specific patient populations such as those with suspected nocturnal hypoglycaemia.
PP6.2.2	Retrospective CGM systems are not currently reimbursed by the NDSS or health insurance funds. These systems are designed to be used continuously over short periods of time (e.g. up to 6 days continuously), to aid profile setting and trouble shooting in glycaemic control.

Chapter 7. Insulin and pharmacological therapies

Question 7.1	
(i) How effective are insulin analogues versus human insulin at reducing hypoglycaemia and HbA _{1c} ? (ii) What is the relative effectiveness between insulin analogues on hypoglycaemia rates and HbA _{1c} ? (iii) What are the cost and cost-effectiveness of insulin analogues on hypoglycaemia rates and HbA _{1c} ?	
Recommendation	
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).
Practice points	
PP7.1.1	Basal and rapid-acting insulin analogues may reduce the risk of hypoglycaemia compared to human insulin.
PP7.1.2	Insulin analogues may be useful in people who have a history of recurrent nocturnal or severe hypoglycaemia.

PP7.1.3	In some people, basal and rapid-acting insulin analogues may improve an individual's HbA _{1c} level without increasing hypoglycaemia.
PP7.1.4	Rapid-acting insulin analogues may be useful in people who match bolus insulin doses to carbohydrate intake.
PP7.1.5	Personal preference and quality of life should be considered when individualising insulin therapy, including analogue therapy versus human insulin.
Question 7.2	
(i) How effective are modern continuous subcutaneous insulin infusion (CSII) pumps versus MDI at reducing hypoglycaemia and HbA _{1c} and improving quality of life (QoL) (DQOL or SF-36 or others)?	
(ii) How effective are sensor-augmented CSII pumps versus MDI at reducing hypoglycaemia and HbA _{1c} , and improving QoL?	
(iii) What are the costs (upfront plus ongoing) and cost effectiveness of treatment with CSII pumps versus MDI?	
Recommendation	
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA _{1c} , reducing hypoglycaemia or improving QoL (Grade C).
Practice points	
PP7.2	Individuals who may be likely to benefit from CSII pump therapy, as part of intensive diabetes management, are: <ul style="list-style-type: none"> • some children and adolescents, including infants and young children, and pregnant women (ideally preconception) • individuals with microvascular complications of diabetes • individuals with reduced hypoglycaemia awareness • individuals (or their supervising adults) with desirable motivational factors; for example, those seeking to improve blood glucose control and having realistic expectations • individuals exhibiting desirable CSII treatment-related behavioural factors, including those who: <ul style="list-style-type: none"> - are able to perform carbohydrate counting - are currently undertaking four or more blood glucose tests per day - have reliable adult supervision (in paediatrics), and a history of good self-management skills (in adults) - are able to master the technical skills of CSII - are reliable in follow-up health care.
Question 7.3	
How effective is metformin plus insulin versus insulin alone at achieving glycaemic control (HbA _{1c} targets), reducing body weight, and reducing insulin requirement?	
Recommendation	
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).
Practice points	
PP7.3.1	Metformin may be considered in individuals who have a high insulin requirement (e.g. overweight or obese subjects with total daily insulin dose at or above 2.0 IU/kg body weight), although the evidence demonstrates only a modest overall reduction in insulin requirement.
PP7.3.2	Since metformin may contribute to lactic acidosis development in metabolically unstable patients, it is relatively contraindicated in people who are at high risk of developing diabetic ketoacidosis or have high alcohol consumption.
PP7.3.3	Metformin is not contra-indicated in individuals with type 1 diabetes and co-existing polycystic ovary syndrome, and may be used to help induce ovulation.
PP7.3.4	Use of metformin in type 1 diabetes is not approved by the Therapeutic Goods Administration and is an 'off-label' indication in Australia. Prescribers should be aware that long-term adverse effects of metformin include an increased risk of vitamin B-12 deficiency, which should be monitored.

Chapter 8. Health Care Delivery

Question 8.1	
What is the effectiveness of ambulatory care versus hospital inpatient care of people with newly diagnosed disease?	
Recommendation	
R8.1	Children and adolescents presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).
Practice points	
PP8.1.1	Groups for whom inpatient management is necessary at diagnosis include: <ul style="list-style-type: none"> • individuals with diabetic ketoacidosis, significant comorbidities, inadequate social support or mental health issues • children under 2 years of age • those in geographically remote areas • non-English speakers.
PP8.1.2	In adults, ambulatory care at diagnosis is considered to be routine unless there are specific issues.
HbA _{1c} , glycated haemoglobin	
Question 8.2	
What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?	
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice point	
PP8.2	Technological mechanisms to support management can be a component of care for rural and remote patients, but should not replace face-to-face clinical care.

Chapter 9. Education and psychological support

Question 9.1	
What is the diagnostic performance of the following screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?	
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice points	
PP9.1.1	Regardless of whether a psychological screening tool is used, people with a suspected mental health disorder should be referred for appropriate assessment.
PP9.1.2	Consideration should be given to the practicality of using specific psychological screening tools in clinical practice (self versus interviewer or clinician administered; length; complexity), reference to more general tools or screening already undertaken, resourcing issues and labelling (as per mental health in general).
PP9.1.3	Diabetes care teams should have appropriate access to mental health professionals to support them in the assessment of psychological functioning in people with type 1 diabetes.
PP9.1.4	In children and adolescents with type 1 diabetes, assessment of developmental progress in all domains (i.e. physical, intellectual, academic, emotional and social development) is advised on a routine basis.

Question 9.2	
What is the effectiveness of education and/or psychological support programs in type 1 diabetes: (i) on metabolic outcomes (ii) on psychological outcomes?	
Recommendation	
R9.2	Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).
Practice points	
PP9.2.1	Educational and psychological interventions should be culturally, developmentally and age appropriate.
PP9.2.2	The multidisciplinary diabetes health-care team should aim to maintain consistent contact with people with diabetes and their families or carers.
PP9.2.3	It is important for the multidisciplinary diabetes team to provide preventive interventions for patients and families (include training parents in effective behaviour-management skills) at key developmental stages, including after diagnosis and before adolescence. The aim of these interventions is to emphasise appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control(Delamater 2009).
PP9.2.4	Diabetes care teams should have appropriate access to mental health professionals to support them in the delivery of psychological support.
PP9.2.5	Flexible intensive insulin therapy programs, such as DAFNE, aim to provide dietary freedom for people with type 1 diabetes.

Chapter 10. Nutrition

Question 10.1	
What are the efficacy and safety of (i) regulating or quantifying dietary carbohydrate and (ii) insulin-to-carbohydrate ratios in type 1 diabetes?	
Recommendation	
R10.1	Matching of mealtime insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).
Practice points	
PP10.1.1	An individualised insulin to carbohydrate ratio should be used for individuals using CSII and may be used in those on multiple daily injection therapy as part of a comprehensive education program.
PP10.1.2	Adjusting insulin with carbohydrate quantity has the potential to improve QoL and increase flexibility in food intake in people with type 1 diabetes. However, regularity in meal routines remains important for optimal glycaemic control.
PP10.1.3	Advice on carbohydrate quantity and distribution should take into account an individual's energy requirements, previous dietary and eating patterns, activity levels and insulin regimen.
PP10.1.4	Advice on carbohydrate quantification should be given within the context of a healthy diet to ensure that overall nutritional needs are being met. In contrast, focussing solely on carbohydrate can lead to poor food choices, carbohydrate avoidance and/or insulin omission.
PP10.1.5	Matching insulin to carbohydrate requires comprehensive education in accurate carbohydrate counting, which should be provided by a dietitian experienced in this area.
PP10.1.6	Day-to-day consistency in carbohydrate intake is important for patients who are on fixed insulin regimens.

Question 10.2	
What are the efficacy and safety of low glycaemic index or high-fibre diets in type 1 diabetes?	
Recommendation	
R10.2	Individuals with type 1 diabetes should be educated on low-GI diets (Grade A).
Practice point	
PP10.2.1	GI should not be used in isolation, but with a method of carbohydrate quantification or regulation.
PP10.2.2	High GI food choices combined with low GI food choices can lower the glycaemic impact of a meal.
PP10.2.3	Where possible, high GI food choices should be substituted with moderate or low GI choices.
PP10.2.4	Food choices should also consider other nutritional aspects in addition to GI, with a focus on lower fat, higher fibre, nutrient-dense foods.
Question 10.3	
What are the efficacy and safety of a high protein diet in type 1 diabetes?	
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice points	
PP10.3.1	High-protein/low-carbohydrate diets in children and adolescents may have deleterious effects on growth.
PP10.3.2	High-protein diets, particularly those based on animal protein or red meat, may lead to progression of diabetic nephropathy. Reducing protein intake to levels consistent with the recommended dietary intakes or replacing red meat with vegetable or soy protein may help to reduce the progression of nephropathy.
PP10.3.3	Restricting carbohydrate intake may affect the nutritional adequacy of the diet and may cause hypoglycaemia if insulin therapy is not adjusted accordingly.
PP10.3.4	High-protein, low carbohydrate diets result in ketosis, which may affect blood glucose control and result in dehydration, lethargy and loss of lean body mass.
Question 10.4	
What are the efficacy and safety of modifying dietary fat intake in type 1 diabetes?	
Recommendation	
R10.4	Diets high in monounsaturated fats should not be used routinely in type 1 diabetes (Grade C).
Practice points	
PP10.4.1	Advice on fat intake should include focussing on reducing saturated and trans fat intake, to reduce the risk of cardiovascular disease.
PP10.4.2	Substitution of saturated and trans fats with monounsaturated or polyunsaturated fats should be encouraged.
PP10.4.3	Education on carbohydrate quantification should discourage consumption of high-fat foods, particularly packaged snacks.
PP10.4.4	Advice to lower energy intake, specifically total fat intake, should be given to people with type 1 diabetes who are overweight or obese, or who are at risk of overweight or obesity.

Chapter 12. Complementary and alternative medicines

Question 12.1	
(i) What is the effectiveness of complementary and alternative medicines at achieving metabolic targets? (ii) What are the costs and cost effectiveness of complementary and alternative medicines at achieving metabolic targets?	
Recommendation	
R12.1	CAM should not be used in type 1 diabetes to target metabolic outcomes (Grade C).
Practice points	
PP12.1	Clinicians should ask people about CAM in a nonjudgmental way, and document their use.
PP12.2	People with type 1 diabetes should be aware that there is a lack of evidence for the effectiveness of CAM.
PP12.3	While there is evidence for a low rate of adverse events due to CAM usage, the possibility of adverse interactions between CAM and conventional medicines should be considered.
PP12.4	People who use CAM should be advised not to cease their insulin therapy because of the consequent high risk of diabetic ketoacidosis.

Chapter 13. Maternal pregnancy and fetal outcomes

Question 13.1	
What is the effectiveness of preconception care in women with type 1 diabetes on improving maternal and fetal outcomes?	
Recommendation	
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).
Practice points	
PP13.1.1	Counselling on contraception, pregnancy planning and preconception care should start during adolescence in females with type 1 diabetes.
PP13.1.2	At the time of planning pregnancy, females with type 1 diabetes should be referred to a multidisciplinary diabetes care team with expertise in preconception care. The team should consist of health professionals with an interest and experience in managing diabetes in pregnancy, including an obstetrician, an endocrinologist (or a physician experienced in diabetes care during pregnancy), a diabetes educator and a dietitian.
PP13.1.3	Intensive glycaemic management to optimise and maintain the HbA _{1c} level in a safe manner is an essential component of preconception care. This may take some 3 to 6 months to achieve.
PP13.1.4	There is an increased risk of neural tube defects in pregnancies in type 1 diabetes, so high-dose folic acid (5mg daily) supplementation should be started at least one month before conception, and continued for at least 3 months into the pregnancy.
PP13.1.5	Screening for diabetes complications specifically for diabetic retinopathy and nephropathy, should occur during preconception care.
PP13.1.6	Preconception care should include a strong focus on intensive blood glucose control prior to conception, complications screening, folate supplementation, discussion of smoking and alcohol intake, and review of medications. Statins, ACEI and ARBs are contraindicated in pregnancy.
PP13.1.7	Glycaemic control should be optimised before starting assisted reproduction procedures.

Question 13.2	
What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?	
Recommendation	
	There was insufficient evidence to make a recommendation.
Practice points	
PP13.2.1	Intensive management to achieve and then maintain optimal glycaemic control should occur throughout pregnancy and ideally commence preconception.
PP13.2.2	Care should be provided by a multidisciplinary team experienced in the management of diabetes in pregnancy.
PP13.2.3	The potential benefits of tight glycaemic control should be balanced against the risk of severe hypoglycaemia during pregnancy.
PP13.2.4	For type 1 diabetes in pregnancy a target HbA1c of <6.0% is desirable but unless this can be achieved safely, a conservative target of <7.0% is recommended.

Chapter 14. Contraception

Question 14.1	
What is the effectiveness of hormonal versus non-hormonal contraception in type 1 diabetes?	
Recommendation	
	There was insufficient evidence to make a recommendation.
Practice points	
PP14.1	The relative risk of unplanned pregnancy should be considered against the potential cardiovascular risk associated with systemic hormonal contraceptives.
PP14.2	Non-hormonal contraceptive methods (e.g. IUD methods, condoms) can be effective and are generally well tolerated.
PP14.3	Contraceptive preferences will often differ across women of reproductive age, for example, between an adolescent with type 1 diabetes and a 40–45-year-old woman.
PP14.4	In a stable long-term relationship, male contraception through vasectomy is an effective non-hormonal permanent contraceptive method.

Chapter 16. Hypoglycaemia

Question 16.1	
i)	What are the predictive factors for severe hypoglycaemia?
ii)	What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?
Recommendation	
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).
Practice points	
PP16.1.1	Minimising severe hypoglycaemia is important, including as a component of intensive diabetes management.
PP16.1.2	Intensive diabetes management may increase the risk of severe hypoglycaemia; therefore, some people who have a high risk of severe hypoglycaemia may not be suitable for the usual tight HbA _{1c} targets.
PP16.1.3	Recognised risk factors that increase severe hypoglycaemia risk include alcohol abuse and recreational drug abuse; these should also be addressed in people with type 1 diabetes.
PP16.1.4	Specific management strategies should be implemented for people who have a high risk of severe hypoglycaemia, including those with a history of severe hypoglycaemia or a reduced ability to detect early warning symptoms of hypoglycaemia (i.e. hypoglycaemia unawareness). In cases of hypoglycaemia unawareness, strategies to reduce severe hypoglycaemia include more frequent SMBG, and ensuring that any blood glucose below a certain threshold (e.g. <4 mmol/L) is treated as hypoglycaemia, even in the absence of hypoglycaemic symptoms.
PP16.1.5	A medical practitioner should carefully assess whether a person with type 1 diabetes is fit to drive a motor vehicle, this is required, in particular, to help reduce the risk of motor vehicle crashes due to severe hypoglycaemia. The AustRoads <i>Assessing fitness to drive</i> booklet, should be used as a reference.
Question 16.2	
What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?	
Recommendation	
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.
Practice points	
PP16.2.1	Adverse cognitive effects of acute severe hypoglycaemia and acute severe hyperglycaemia should be avoided during tasks requiring high level cognitive function, such as in school, college or university examinations; or in adolescents and adults during potentially dangerous activities involving occupational health, such as operating heavy machinery or during driving. In some cases, the risk or presence of acute severe changes in blood glucose to very low and possibly very high levels may lead to the need for exemption from or avoidance of the cognitively demanding or high-risk activity.
PP16.2.2	Mild hypoglycaemia and mild hyperglycaemia are common in type 1 diabetes; however, acute severe dysregulation of blood glucose to either extreme that may cause cognitive effects should be avoidable in most people with type 1 diabetes, if due self-care is taken.
PP16.2.3	The blood glucose level at which a person develops cognitive effects from severe hypoglycaemia can vary, related to the degree of chronic glycaemia control and avoidance of severe hypoglycaemia if an episode has occurred during recent weeks to months. In such cases, early warning symptoms of hypoglycaemia that may have been lacking in a person with type 1 diabetes may at least partially return.

Question 16.3	
How can severe hypoglycaemia be prevented?	
Recommendation	
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).
Practice points	
PP16.3.1	Developmentally appropriate structured education programs, such as 'self-study material' video programs and Blood Glucose Awareness Training (BGAT), can be used to help to reduce rates of severe hypoglycaemia.
PP16.3.2	Some programs, such as BGAT, can be delivered as individual or group programs.
PP16.3.3	Where resource constraints apply, structured education should be offered preferentially to individuals at highest risk of and from severe hypoglycaemia, for example, those with a history of recurrent severe hypoglycaemia, and adults who are motor vehicle drivers.
PP16.3.4	Research into modified programs to prevent severe hypoglycaemia that may require less resource and time input needs to be undertaken. Such research needs documented outcomes, including assessment of optimal time intervals for people to undertake refresher courses.

Chapter 17. Acute complications – diabetic ketoacidosis and sick-day management

Question 17.1	
Does ketone monitoring prevent ketoacidosis or hospital admission?	
Recommendation	
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade C).
Practice points	
PP17.1	Blood ketone measurement is preferred, because it gives a more timely result. However, where blood ketone measurement is not available, urine ketone measurement is the alternative test as part of a comprehensive sick-day management plan.
PP17.2	Blood ketone measurement is preferred in people using CSII.
PP17.3	Blood ketone measurement may be especially useful in very young children or when urine specimens are difficult to obtain.
PP17.4	A comprehensive sick-day management plan should include written guidelines and 24-hour access to clinical advice.
PP17.5	The sick-day management plan should be regularly reviewed by the patient and diabetes health-care professional.

Chapter 18. Microvascular and macrovascular complications

Question 18.1	
What is the effect of intensive glycaemic management on microvascular and macrovascular complications?	
Recommendation	
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).
Practice points	
PP18.1.1	Intensive glycaemic control refers to an implemented strategy of intensive glycaemic management and is only achieved by a 'package' of methods, including MDI or CSII, frequent insulin dose adjustment, blood glucose level monitoring at least four times per day, weekly measurement of 3am blood glucose levels, formal diabetes education, medical nutrition therapy and physical activity advice.
PP18.1.2	The generalisability of implementing an intensive glycaemic control strategy may be limited by the strict inclusion criteria in the clinical trials undertaken. The potential benefit of a strategy of intensive glycaemic control needs to be individualised as much as is practical.
Question 18.2	
(i) How effective are antihypertensive agents at controlling blood pressure in type 1 diabetes? (ii) How effective are antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Recommendation	
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B).
Practice points	
PP18.2.1	For patients who are intolerant of ACEI, ARBs can be used as an alternative treatment for the secondary prevention of nephropathy.
PP18.2.2	On the basis of the systematic evidence, including data in adolescents(Cook et al 1990), ACEI in type 1 diabetes can control albuminuria in normotensive microalbuminuria; however, there are currently restrictions from the Therapeutic Goods Administration to be considered in their use in this setting of normotension.
PP18.2.3	Tight control of blood pressure is of critical importance in limiting the progression of retinopathy and nephropathy. The general blood pressure target is <130/80 mmHg and <125/75 mmHg in the presence of 1 g daily or more of proteinuria.
PP18.2.4	ACEI and ARBs are contraindicated in pregnancy.
PP18.2.5	A small study has raised concerns that oral contraceptive use in women with type 1 diabetes may limit the efficacy of ACEI and ARB and contribute to macroalbuminuria. Large prospective studies are required to further investigate this relationship.
Question 18.3	
What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?	
Recommendation	
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).
Practice points	
PP18.3.1	As global macrovascular risk in type 1 diabetes is high in adults, statins should be commenced early in the disease course and before the development of cardiovascular disease.

PP18.3.2	Statin therapy can be used after Tanner stage II in boys and after menarche in females. In high-risk vascular disease states (e.g. hereditary LDL receptor deficiency), statins may be indicated from the age of 8 years.
PP18.3.3	Statin therapy is contraindicated in pregnancy, and reliable contraceptive methods should be used in females of reproductive age who are on statin treatment.
PP18.3.4	The benefit of statin therapy in people with end-stage renal failure (including in those with type 1 diabetes) has not been confirmed; however, it is prudent to use low-dose statin treatment in this group, which is at particularly high risk of cardiovascular disease.

Chapter 20. Other complications and associated conditions

Question 20.1	
How and how often should people with type 1 diabetes be screened for coeliac disease?	
Recommendation	
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).
Practice points	
PP20.1.1	Adults with newly diagnosed type 1 diabetes should be screened for coeliac disease at diagnosis.
PP20.1.2	Adults with type 1 diabetes who have not been previously screened should be screened for coeliac disease.
PP20.1.3	Children and adolescents should be rescreened for coeliac disease at least once in the first five years after diagnosis.
Question 20.2	
How and how often should people with type 1 diabetes be screened for thyroid disease?	
Recommendation	
R20.2	Screening for thyroid dysfunction and testing for antibodies to thyroid peroxidase (TPO Ab) should be performed at diagnosis of type 1 diabetes; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).
Practice points	
PP20.2.1	Tests for TSH should be repeated at least yearly in those with anti-thyroid antibodies at diagnosis.
PP20.2.2	Tests for TSH should be repeated at least 2-yearly in all other patients with type 1 diabetes.
PP20.2.3	Women planning pregnancy should have a blood test for TSH preconception and in the first trimester.
PP20.2.4	Women who are TPO Ab positive should be tested postpartum for thyroid dysfunction.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BGAT, blood glucose awareness training; BITES, Brief Intervention in Type 1 diabetes, Education for Self-efficacy; CAM, complementary and alternative medicine; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DAFNE, dose adjustment for normal eating; DCCT, Diabetes Complications and Control Trial; DKA, diabetic ketoacidosis; DQOL, diabetes quality of life; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient; LDL, low density lipoprotein; MDI, multiple daily injections; NDSS, National Diabetes Services Scheme; QoL, quality of life; RCT, randomised controlled trial; SF-36, short-form health survey; SMBG, self-monitored blood glucose; TPO Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; VLDL, very low density lipoprotein; β -OHB, beta-hydroxybutyrate

1 Introduction

1.1 Development of the guidelines

The *Clinical practice guidelines: Type 1 diabetes in children and adolescents* (APEG 2005) were approved by the National Health and Medical Research Council (NHMRC) in 2005. The guidelines were aimed at health-care professionals involved in the care of children and adolescents with type 1 diabetes. Although the document included transition to adult care, it did not address the needs of adults with type 1 diabetes. In addition, the guidelines were developed at a time when management and technologies were less well developed than they are today. Thus, revision of the 2005 guidelines was needed because of:

- evolving technologies, including continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) systems (Bergenstal et al 2010; Misso et al 2010)
- greater use of insulin analogues and multiple daily injection (MDI) regimens (Singh et al 2009)
- changes to medical nutrition therapy including increased use of flexible insulin dose adjustment for carbohydrate quantity (Thomas and Elliott 2009)
- increasing evidence base for the importance of blood glucose control for the prevention of macrovascular disease and long-term complications (Nathan et al 2005)
- greater awareness of psychosocial aspects of type 1 diabetes (Northam et al 2010)

Therefore, the Australasian Paediatric Endocrine Group (APEG) and the Australian Diabetes Society (ADS), on behalf of the Australian Government Department of Health and Ageing (DoHA), agreed to update the existing guideline, and extend the scope to include adults with type 1 diabetes, including pregnancy.

1.2 Scope

The scope of the guidelines is to provide evidence based guidance to the clinician managing children, adolescents and/or adults with type 1 diabetes. The guidelines provide evidence based recommendations and practice points for many, but not all areas of clinical care in type 1 diabetes. The areas for which systematic reviews have been undertaken are clearly noted in the executive summary and throughout the document, where a clinical question has been asked. These are summarised below:

- Interventions for the prevention of type 1 diabetes
- Prevalence of psychological disorders in people with type 1 diabetes
- The impact of type 1 diabetes on cognitive performance
- Blood glucose monitoring
- Insulin and pharmacological therapy, including insulin analogues, continuous subcutaneous insulin infusion (CSII) and metformin
- Health care delivery (ambulatory care)
- Education and psychological support
- Nutrition therapy

- Complementary and alternative medicines
- Maternal pregnancy and fetal outcomes – effectiveness of preconception care and blood glucose control during pregnancy
- Hormonal versus non-hormonal contraception
- Prediction and prevention of hypoglycaemia and its effects on cognitive function
- Ketone monitoring
- Prevention and management of microvascular and macrovascular complications
- Screening for other complications and associated conditions (coeliac and thyroid disease)

There are some aspects of type 1 diabetes that were not systematically reviewed in this document; in most cases this was because (i) the information was epidemiological or background information (ii) the EAG were aware of the existence of contemporary national or international evidence based guidelines, including the NHMRC approved Guideline on Prevention, Identification and Management of Foot Complications in Diabetes (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011) and those from the International Society for Pediatric and Adolescent Diabetes (ISPAD 2009), the American Diabetes Association (ADA 2010) and the National Institute of Clinical Excellence (NICE 2010) or (iii) the EAG considered the subject to be beyond the scope of the current guidelines, but narrative text was required to provide context. The reader should refer to these guidelines for further details and information on grading of evidence. For chapters and sections that were not systematically reviewed in the development of these guidelines, it is clearly noted and there are no recommendations, clinical practice points or directive clinical guidance arising from these sections. These sections include:

- The impact of type 1 diabetes on growth and physical development
- Urban versus rural care of type 1 diabetes in Australia
- The cost burden of type 1 diabetes to the individual and society
- Role of major trials in advancing clinical care in blood glucose management
- Exercise in type 1 diabetes
- Effectiveness of insulin pumps and CGMS during pregnancy
- Diabetes complications monitoring during pregnancy
- Transition of care from paediatric to adult health services
- Efficacy and safety of hypoglycaemia treatments
- Management of sick days and diabetic ketoacidosis
- Prediction of cardiovascular disease risk in type 1 diabetes
- Frequency of screening for complications

1.3 Purpose, healthcare settings and target audience

The purpose of the current document is to provide a national evidence based guideline for management of type 1 diabetes in children, adolescents and adults. The guidelines are to be used in both the hospital and ambulatory healthcare setting. While most type 1 diabetes is managed by a multidisciplinary specialist health-care professional team, particularly for

children and adolescents, the guideline also targets primary care physicians. This includes the rural and regional setting, where diabetes care may be provided by a locally based paediatrician, physician or a general practitioner (GP), or on a shared care basis with a multidisciplinary diabetes care team.

1.4 Population groups

The target population is children, adolescents and adults with type 1 diabetes. Specific subgroups (e.g. children, adolescents, adults) were considered separately for all systematically reviewed questions and where the evidence differed, evidence statements, recommendations and practice points were developed for specific groups. There was a paucity of information found on management of type 1 diabetes for Aboriginal and Torres Strait Islander peoples. In particular sections (e.g. health care delivery), specific considerations for Aboriginal and Torres Strait Islander peoples have been included.

1.5 Governance structure

A multilevel management structure was established to coordinate the development of the type 1 diabetes guidelines. The structure consists of:

- an executive consisting of co-chairs from APEG and ADS, and executive members responsible for the overall development and governance of the entire project
- an Expert Advisory Group (EAG) responsible for clinical oversight of the guidelines, including appraisal of evidence
- project officers responsible for systematic reviews of the literature
- expert methodological consultants to provide advice and mentoring to the systematic reviewers and the EAG; and to ensure that the development process and the guidelines produced comply with NHMRC requirements (NHMRC 2007)
- a medical and technical editor

DoHA provided project funding, while project management was performed by the co-chairs. Appendix A provides details of the membership of the executive and EAG involved in governance. Details of how the guidelines will be implemented and updated are provided in Chapter 22.

1.6 Structure of the document and related materials

1.6.1 The document

The guideline developers produced recommendations and practice points, as follows:

- *recommendations* – based on evidence from the systematic reviews
- *practice points* – based on consensus decision-making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but clinicians require guidance to ensure good clinical practice.

The recommendations and practice points are given in the relevant sections of Chapters 3–20, and summarised in the Executive Summary.

The remainder of the document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the EAG; these chapters also give recommendations and practice points, as appropriate (Chapters 3–20)
- recommendations for further research (Chapter 21)
- information on implementing, evaluating and maintaining the guidelines (Chapter 22).

The document also includes appendices that provide information on membership of the Expert Advisory Group (the governance body for guideline development), a process report, evidence matrixes and useful resources for health professionals and people with type 1 diabetes. Finally, the document contains a list of abbreviations and acronyms, and a list of references.

1.6.2 Related materials

After the public consultation, materials relevant to health professionals and health consumers will be developed to accompany these guidelines; these materials will be available online and in print.

The technical report that underpins this document is also available online. This includes background information and the results of the systematic review pertaining to the clinical questions posed within this guideline, including results of the literature searches, study quality appraisal, NHMRC evidence statement forms (NHMRC 2009) and evidence summaries for the individual studies.

2 Methods

The development of evidence-based clinical practice guidelines involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence (NHMRC 1999; NHMRC 2007; NHMRC 2009). The methods used in applying this process to the development of these guidelines are outlined below. A summary of the overall guideline development process is given in Appendix B (Process report).

2.1 Clinical research questions – development and details

Between July 2009 and March 2010, the clinical research questions were developed, prioritised, combined and refined by the Expert Advisory Group (EAG) and project officers, in consultation with expert methodological consultants (Appendix A). The process resulted in different types of questions, as shown in Table 2.1.

Table 2.1 Details of question types

Question type ^a	Answered based on	Uses
Interventional	Systematic review	Used to develop: <ul style="list-style-type: none">• recommendations• practice points
Diagnostic accuracy	Systematic review	Used to develop: <ul style="list-style-type: none">• recommendations• practice points
Prognostic	Systematic review	Used to develop: <ul style="list-style-type: none">• recommendations• practice points
Aetiological	Systematic review	Used to develop: <ul style="list-style-type: none">• recommendations• practice points

^a See Section 2.3 for explanation of question types

The systematically reviewed questions were developed by the EAG, with the aim of answering clinically relevant areas of uncertainty; however, it was recognised that, in some areas, there was little or no high-quality published evidence. Details of research question criteria are presented in the technical report that accompanies this document.

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken with the aim of answering high-priority questions relevant to the care of individuals with type 1 diabetes. To answer these questions, a broad search strategy was designed, in consultation with the expert methodological consultants, as detailed in the accompanying technical report. Searches were conducted by the project officers in relevant electronic databases and bibliographies of studies identified as appropriate. In addition, publications were identified by members of the EAG. The systematic reviews included only data from studies that met the prespecified inclusion criteria, were of adequate quality and were published before December 2010. Identification of relevant evidence and assessment of evidence was conducted as detailed in the *NHMRC*

standards and procedures for externally developed guidelines (NHMRC 2007). Appraisal of evidence, including assessment of quality and risk of bias, was conducted as outlined in Section 2.2.2 below (NHMRC 2000).

2.2.2 Study Assessment Criteria

A. Level of Evidence

See Table 2.7 (NHMRC Levels of Evidence).

B. Quality Criteria

Systematic reviews

- Were the questions and methods clearly stated?
- Were comprehensive search methods described?
- Were explicit methods used to determine which studies were included in the review?
- Was the methodological quality of primary studies assessed?
- Was selection and assessment of primary studies reproducible and free from bias?
- Were differences in individual study results adequately explained?
- Were the results of primary studies combined appropriately?
- Were the reviewers' conclusions supported by data cited?
- Were sources of heterogeneity explored?

Randomised controlled trials

- Were the setting and study subjects clearly described?
- Was assignment randomised and similar between groups documented?
- Was allocation to study groups adequately concealed from subjects, investigators and recruiters including blind assessment of outcome?
- Were all clinically relevant outcomes reported?
- Were >80% of subjects who entered the study accounted for at its conclusion?
- Were they analysed in the groups to which they were randomised (intention to treat)?
- Were both statistical and clinical significance considered?

Population studies

- Were the setting, population and selection criteria described?
- Were the subjects representative of the population?
- Were the studies prospective, cross-sectional, or retrospective?
- Were clinically relevant outcomes reported?
- Were >80% of subjects accounted for in results?
- Were the analyses appropriate?

Cohort studies

- How were subjects selected for the cohort - comparison and control groups?
- Were the recruitment setting, diagnostic criteria, disease severity, co-morbidity and demographics documented?
- Was the referral pattern described?
- Was referral or diagnostic access bias avoided?
- Were the two groups comparable on demographic characteristics and clinical features?
- Were >80% of subjects entered accounted for in results and clinical status known?
- Were objective outcome criteria developed and used?
- Was outcome assessment blind?
- Was follow-up complete and were there exclusions from the analysis?

Case-control studies

- How were cases selected?
- How were controls selected?
- Was the definition of cases adequate?
- Are the two groups comparable on demographic characteristics and important potential confounders?
- Was ascertainment of exposure to the factor of interest blinded to case/control status?
- Were all selected subjects included in the analysis?

C. Quality – Rating

The following criteria were used to rate the quality of each study against the study type criteria listed above:

High	All or all but one of the criteria were met
Medium	2 or 3 of the criteria were not met
Low	4 or more of the criteria were not met

D. Size of the effect

The following criteria were used for classifying size of the effect (NHMRC 2000):

Ranking	Clinical Importance of benefit
1	A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention
2	The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects
3	The confidence interval does not include any clinically important effects
4	The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect

E. Relevance

The following criteria were used for classifying the relevance of the evidence (NHMRC 2000):

Ranking	Relevance of the evidence
1	Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival
2	Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention
3	Evidence of an effect on proven surrogate outcomes but for a different intervention
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population
5	Evidence confined to unproven surrogate outcomes.

2.2.3 Background material and other guidelines

Materials used for the narrative text – sections that were not systematically reviewed and did not include any clinical recommendations – were gathered by the project officers under the supervision of the EAG executive.

Guidelines from Australia that were used included the Australian Diabetes Society (Australian Diabetes Society 2008; Cheung et al 2009b), which graded evidence according to NHMRC levels of evidence (NHMRC 2000), and the NHMRC approved National Evidence-Based Guideline on Prevention, Identification and Management of Foot Complications in Diabetes (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011), which used the more recent additional levels of evidence and grades (NHMRC 2009). Reference is also made to the Queensland Health Best Practice Guidelines for Transition of Young People with Diabetes from Paediatric to Adult Care (Lang 2008), which were not systematically reviewed, and the Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy (McElduff et al 2005), which were systematically reviewed but did not make graded recommendations.

International guidelines sourced included the American Diabetes Association (ADA), the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the National Institute of Clinical Excellence (NICE 2010). The grading system used by the ADA and ISPAD is shown in Table 2.2 (ADA 2010) and those used in the NICE guidelines, which used separate grading schemes for the recommendations for adults and children, are shown in Tables 2.3 and 2.4 (NICE 2010).

Table 2.2 ADA grading system for clinical practice recommendations

Level of evidence	Description
A	<p>Clear evidence from well-conducted, generalisable, randomised, controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted multicentre trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis <p>Compelling nonexperimental evidence, i.e. “all-or- none” rule developed by the Centre for Evidence-based Medicine at Oxford</p> <p>Supportive evidence from well-conducted, randomized, controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	<p>Supportive evidence from well-conducted cohort studies:</p> <ul style="list-style-type: none"> • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies <p>Supportive evidence from a well-conducted case-control study</p>
C	<p>Supportive evidence from poorly controlled or uncontrolled studies</p> <ul style="list-style-type: none"> • Evidence from randomised clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias such as case series with comparison to historical controls • Evidence from case series or case reports <p>Conflicting evidence with the weight of evidence supporting the recommendation</p>
E	Expert consensus or clinical experience

Table 2.3 NICE grading system for clinical practice recommendations for children and young people with type 1 diabetes, adapted from (Blanchard et al 1997)

Recommendation grade	Evidence
A	Directly based on category I evidence
B	<p>Directly based on:</p> <ul style="list-style-type: none"> • category II evidence, or • extrapolated recommendation from category I evidence
C	<p>Directly based on:</p> <ul style="list-style-type: none"> • category III evidence, or • extrapolated recommendation from category I or II evidence
D	<p>Directly based on:</p> <ul style="list-style-type: none"> • category IV evidence, or • extrapolated recommendation from category I, II, or III evidence
Evidence category	Source
I	<p>Evidence from:</p> <ul style="list-style-type: none"> • meta-analysis of randomised controlled trials, or • at least one randomised controlled trial
II	<p>Evidence from:</p> <ul style="list-style-type: none"> • at least one controlled study without randomisation, or • at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case– control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Table 2.4 NICE grading system for clinical practice recommendations for adults with type 1 diabetes

Hierarchy of Evidence		Grading of recommendations	
Ia	evidence from meta-analysis of randomised controlled trials	A	based on category I evidence
Ib	evidence from at least one randomised controlled trial		
IIa	evidence from at least one controlled study without randomisation	B	based on category II evidence or extrapolated from category I
IIb	evidence from at least one other type of quasi experimental study		
III	evidence from non- experimental descriptive studies, such as comparative studies, correlation studies and case control studies	C	based on category III evidence or extrapolated from category I or II
IV	evidence from expert committee reports or opinions and/or clinical experience of respected authorities		

Background materials were also sourced from medical textbooks, published original research and review articles, and other relevant medical literature; however, systematic review processes were not applied. The sections and chapters researched in this manner are noted below each question throughout the guideline.

2.3 Development of evidence statements, recommendations and practice points

For each research question addressed by the systematic review, the body of evidence was consolidated into evidence statements and rated by the EAG as detailed in the evidence matrix shown in Table 2.5 (NHMRC 2009). The matrix considers five domains: evidence base, consistency, clinical impact, generalisability and applicability. For included studies, the first two components were derived directly from the literature identified for each research question; for assessment of the last three components (clinical impact, generalisability and applicability), guidance was provided by the EAG. To ensure that guidelines were based on the best available evidence, studies of higher levels of evidence (i.e. Levels I or II) were included in preference to those presenting lower levels (i.e. Levels III or IV) of evidence (Table 2.5). This minimises the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence for any of the primary outcomes was not available in higher-level studies.

Table 2.5 Body of evidence matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base ¹	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review/multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and any inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around a clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guideline	Population/s studied in the body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population for the guideline
Applicability	Directly applicable to the Australian health-care context	Applicable to the Australian health-care context with a few caveats	Probably applicable to the Australian health-care context with some caveats	Not applicable to the Australian health-care context

Source: NHMRC (2009)

¹ Level of evidence determined from the NHMRC evidence hierarchy – see Table 2.6

Evidence statements were only transformed into ‘action-oriented’ recommendations where:

- the body of evidence was sufficient; that is, wherever the evidence yielded support for recommendations of at least NHMRC grade C (see Table 2.6)
- the question type was interventional (i.e. it evaluated the effectiveness of an intervention)

The recommendations were carefully worded to reflect the strength of the body of evidence.

Table 2.6 Definitions of NHMRC grades for recommendations

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC (2009)

Table 2.7 NHMRC levels of evidence

Level	Intervention	Diagnostic accuracy	Prognosis
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study	A retrospective cohort study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease

Source: NHMRC (2009)

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation, the EAG used an expert consensus-based process to develop practice points related to the relevant clinical question, to guide clinical practice. Using the same consensus-based method, practice points were also developed where the EAG determined that additional information was required to supplement formulated recommendations to guide clinical practice. For prognostic and aetiological questions, the evidence base only provided an indication of the risk associated with a particular factor; thus, it was not possible to make an evidence-based recommendation for a change in practice. Instead, the EAG again used a consensus-based process to develop practice points to guide practice. For sections where a systematic review had not been undertaken, the narrative text provides background information for the clinician and reference to contemporary guidelines, as appropriate.

2.4 Description of public consultation

Public consultation was conducted from Monday 7 February to Friday 10 March 2011, during which time the draft guidelines were available on the websites of the Australian Paediatric Endocrine Group (APEG) and Australian Diabetes Society (ADS). Notification was posted in The Australian national newspaper, and a range of stakeholders, committees, working groups and interested people were invited to provide submissions. An electronic feedback form was provided to facilitate submissions.

3 Natural history and prevention

3.1 Introduction

The typical clinical course of type 1 diabetes includes a preclinical phase, presentation of diabetes (at which time patients are usually symptomatic of hyperglycaemia), a partial remission or honeymoon phase, and a continuing requirement for insulin therapy (Haller et al 2005). In the absence of insulin therapy, patients with type 1 diabetes will eventually progress to metabolic decompensation and life-threatening diabetic ketoacidosis (DKA) (Balasubramanyam et al 2008). Over the course of time, acute and chronic complications of diabetes occur in most people with type 1 diabetes. On average, the lifespan of people with childhood onset type 1 diabetes is shorter than that of the general population (Dawson et al 2008; Secrest et al 2010a), although there has been improvement across recent decades and the 20 year mortality rate for people with type 1 diabetes without renal disease, is comparable to the general population (Nishmura et al 2001).

3.2 Epidemiology

In most western countries, type 1 diabetes accounts for more than 90% of childhood and adolescent diabetes, although less than half of people with type 1 diabetes are diagnosed before the age of 15 years (Craig et al 2009a). Type 1 diabetes incidence varies greatly between different countries, within countries and between different ethnic populations. Mean annual incidence rates for childhood type 1 diabetes (0–14 years age group) across the world have varied from fewer than 1 per 100 000 person years to more than 60 per 100 000 person years in recent decades (Diamond Project Group 2006; Harjutsalo et al 2008; Patterson et al 2009). In Australia, the incidence of type 1 diabetes among 0–14-year-olds is approximately 22 per 100 000 person years (Catanzariti et al 2009). This rate is considered very high compared with available data from other countries; Australia ranks in the top 10 countries for type 1 diabetes globally (Craig et al 2009a). Rates of type 1 diabetes also vary within Australia (Haynes et al 2004; Taplin et al 2005) and across different ethnic groups. However, the incidence of type 1 diabetes among indigenous Australian children is similar to that of Caucasian children (Craig et al 2007).

The mean age of onset of type 1 diabetes in Australian children is approximately 8 years of age (Catanzariti et al 2009). Incidence increases gradually throughout childhood, with a peak incidence during early adolescence (Craig et al 2009a) that coincides with puberty. Type 1 diabetes is very uncommon in children aged < 1 year and when diabetes occurs in an infant aged < 6 months (termed 'neonatal diabetes'), it usually results from the inheritance of a mutation or mutations in a single gene (Hattersley et al 2009). The incidence of type 1 diabetes is similar between boys and girls in Australia, although some countries have reported a higher incidence in boys (Patterson et al 2009). The prevalence of type 1 diabetes in childhood is approximately 1 in 300.

The incidence of type 1 diabetes has increased in most western countries and many developing nations in recent decades (Diamond Project Group 2006; Harjutsalo et al 2008; Patterson et al 2009). In Australia, the average increase was 2.8% per year from 2000 to 2006 (Catanzariti et al 2009). The rising incidence of type 1 diabetes is associated with an increased proportion of people with low-risk human leukocyte antigen (HLA) genotypes (Fourlanos et al 2008), which suggests an increasing role for the environment in the pathogenesis of type 1 diabetes (see section 3.3).

3.3 Preclinical diabetes

In the months or years before clinical presentation of type 1 diabetes, one or more autoantibodies can be detected as markers of β -cell autoimmunity. These include insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT-8). It is clear from prospective studies of prediabetes that islet autoimmunity can be transient; however, the presence of persistently raised levels of one or more islet antibodies confers an increased and incremental risk of progression to type 1 diabetes (Orban et al 2009).

Genetic risk markers can further assist in quantifying risk of progression to type 1 diabetes. More than 40 type 1 diabetes susceptibility alleles have been identified (Barrett et al 2009); of these, 10 genes can be singled out as strong causal candidates, and there is significant evidence for linkage with the HLA region on chromosome 6p21.3 (LOD score 213.2) (Concannon et al 2009). HLA alleles that confer an increased risk of type 1 diabetes include HLA DRB1 03-DQA1*0501-DQB1* 0201 and HLA DRB1 04-DQA1*0301-DQB1* 0302, while alleles that confer protection include HLA DR02-DQA1*0102-DQB1* 0602. In the absence of such a protective allele, an individual aged under 45 years has a 25–50% 5-year risk of type 1 diabetes in the presence of two or more islet antibodies (Orban et al 2009).

Genetic testing alone cannot be used to predict development of type 1 diabetes, particularly given that the relative frequency of high-risk HLA class II genotypes in Australian children with type 1 diabetes has decreased in recent decades (Furlanos et al 2008). It is currently accepted that most cases of type 1 diabetes result from an interplay between genetic predisposition or environmental factors; however, the environmental triggers (viral, dietary or chemical) that initiate pancreatic β -cell destruction remain largely unknown. Enterovirus infection has been associated with development of diabetes-associated autoantibodies in some populations (Stene et al 2010; Oikarinen et al 2011; Yeung et al 2011), and enteroviruses have been detected in the islets of people with type 1 diabetes (Richardson et al 2009). Early introduction of cow's milk protein (Knip et al 2010) and weight gain in early life (Couper et al 2009) are also putative triggers for autoimmunity and type 1 diabetes. In the absence of a proven intervention to prevent progression to type 1 diabetes (see Section 3.4 below), screening or intervention in the preclinical phase should be confined to defined clinical studies.

3.4 Interventions to delay or prevent the onset of type 1 diabetes

Question 3.1

What interventions delay or prevent the onset of type 1 diabetes?

The detailed systematic review of this question is in Chapter 3 of the accompanying technical report and the evidence matrix is in Section C3 of Appendix C

The aim of intervention before type 1 diabetes onset is to prevent (primary prevention) or arrest (secondary prevention) immune-mediated β -cell destruction, thereby preventing or delaying clinical disease. It is essential to identify people at risk of type 1 diabetes for such interventions. The number of positive autoantibodies is highly predictive of type 1 diabetes (Orban et al 2009). In the presence of impaired first-phase insulin response (FPIR) to intravenous (IV) glucose, and islet autoantibodies, the projected 5-year risk of type 1 diabetes is greater than 50%; even among people with a normal FPIR, the 5-year risk of type 1 diabetes is greater than 25% (Skyler 2008).

Most intervention studies have targeted either islet autoantibody-positive first-degree relatives, or infants born with a first-degree relative with type 1 diabetes and/or high -risk HLA type, because of their increased risk of type 1 diabetes compared with the general population. Multicentre randomised controlled trials (RCTs) using nicotinamide, parenteral insulin, oral insulin or intranasal insulin, and the elimination of cow's milk protein from infant feeding have been undertaken in recent years, with the aim of preventing type 1 diabetes. The outcomes of these studies are summarised below.

3.4.1 Insulin

Five RCTs examined progression to type 1 diabetes incidence among autoantibody-positive first-degree relatives after exposure to intranasal, oral, IV or subcutaneous (SC) plus IV insulin (Fuchtenbusch et al 1998; DPT-1 Study Group 2002; Harrison et al 2004; Skyler et al 2005; Nanto-Salonen et al 2008). Two of these studies were pilot studies (Fuchtenbusch et al 1998; Harrison et al 2004); the Australian pilot (Harrison et al 2004) was not designed to answer the clinical question asked here. Only one study found a delayed time to development of diabetes (5 years vs 2.3 years, $p < 0.03$), but diabetes incidence was not reported, and the study was underpowered to detect a reduction in diabetes risk from 80% to 30% (Fuchtenbusch et al 1998). In a post-hoc analysis of participants in the oral insulin study in the Diabetes Prevention Trial 1 (DPT-1) who had an IAA level of at least 80 nU/mL ($n = 263$), the proportion who developed diabetes was 6.2% per year in the oral insulin group and 10.4% per year in the placebo group (hazard ratio [HR] 0.57, 95% confidence interval [CI]: 0.36 to 0.89, $p = 0.015$) (Skyler et al 2005). The estimated delay in developing diabetes was 4.5 years. On the basis of this analysis, another large oral insulin prevention study is currently being conducted by the Type 1 Diabetes TrialNet, in relatives with characteristics similar to those of the DPT-1 subgroup (Type 1 Diabetes TrialNet 2010).

3.4.2 Nicotinamide

Four studies have examined the effects of nicotinamide on the development of type 1 diabetes (Lampeter et al 1998; Gale et al 2004; Cabrera-Rode et al 2006; Olmos et al 2006). Three found no difference between treatment and placebo groups, while in the study of 24 participants from Chile (Olmos et al 2006), the 60-month cumulative probability of staying diabetes free was 100% in the nicotinamide group and 62.5% (95%CI: 17 to 100) in the placebo group ($p = 0.048$). However, this study did not have development of diabetes as an *a priori* outcome measure. There is currently insufficient evidence to support the use of nicotinamide for the prevention of type 1 diabetes.

3.4.3 Day-care exposure

A systematic review of case-control studies tested the hypothesis that increased early contact with infectious agents, measured by day-care exposure, would decrease the risk of type 1 diabetes in childhood (Kaila and Taback 2001). Day-care exposure appeared to have a protective effect in the subgroup of children diagnosed with type 1 diabetes before the age of 5 years (OR 0.6, 95%CI: 0.5 to 0.8). However, this result was based on only two studies, and the degree of heterogeneity between the other primary studies examined in the review was too high to allow reliable summary results overall.

3.4.4 Vitamin D

The metabolically active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-OHD), regulates the expression of more than 200 genes, including those related to apoptosis and immune modulation. The gene that encodes 1 α hydroxylase, the enzyme that converts 25-hydroxyvitamin D3 (25-OHD) to 1,25-OHD, is a recently described type 1 diabetes

susceptibility gene (Bailey et al 2007). It has been suggested that changes in vitamin D intake during recent decades have contributed to the recent trends in the increased incidence of type 1 diabetes. A systematic review of observational studies examined whether vitamin D supplementation in infancy reduced the risk of type 1 diabetes in later life (Zipitis and Akobeng 2008). Meta-analysis of data from case–control studies showed that the risk of type 1 diabetes was significantly reduced in infants supplemented with vitamin D compared to those who were not supplemented (pooled OR 0.71, 95%CI: 0.60 to 0.84). There was also some evidence of a dose–response effect, with those using larger amounts of vitamin D being at lower risk of developing type 1 diabetes. However, the high level of bias in these studies limits the applicability of the results. There have been no RCTs to show whether the observed associations between low vitamin D and type 1 diabetes risk are causal.

3.4.5 Summary

No trial has successfully demonstrated prevention of type 1 diabetes. There is some evidence from post-hoc analysis of DPT-1 that oral insulin may slow progression from pre-type 1 to type 1 diabetes in patients with high-titre IAA. This is currently being addressed by an oral insulin trial (Type 1 Diabetes TrialNet 2010). Several other prevention trials are also underway. INIT-II is an Australian multicentre double blind, placebo-controlled RCT of intranasal insulin in children and young adults at risk of type 1 diabetes. The Trial to prevent type 1 diabetes in the Genetically at Risk (TRIGR) is an international multicentre trial (including Australia) that aims to establish whether weaning to a highly hydrolysed formula in infancy subsequently reduces the risk of type 1 diabetes in ‘at-risk’ children (Akerblom 2010). The results of the pilot trial for TRIGR, conducted in Finland, showed that intervention with a hydrolysed formula during infancy halved the risk of development of one or more islet autoantibodies (HR 0.51, 95%CI: 0.28 to 0.91) (Knip et al 2010). However, whether hydrolysed formula or other interventions can prevent progression to type 1 diabetes (as opposed to islet autoimmunity) is presently unknown.

Evidence statement	
Q3.1	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.
Recommendation	
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).
Practice point	
PP3.1	Interventions aimed at delaying or preventing the onset of type 1 diabetes should only be used in a research setting.

3.5 Presentation of diabetes

Clinical presentation at diagnosis can vary widely in people with type 1 diabetes, and age at presentation is an important factor influencing presentation. At one extreme are those presenting with severe DKA who require hospitalisation, intensive rehydration and IV insulin infusion. At the other extreme are those without symptoms of hyperglycaemia, who may be detected incidentally. There are certain clinical scenarios in which the diagnosis of type 1 diabetes may be delayed, particularly in children:

- very young children may present with severe DKA because of a more rapid onset of severe insulin deficiency, and because the symptoms of polyuria and polydipsia may not be apparent to the parent or clinician
- hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from DKA)
- abdominal pain associated with ketoacidosis may simulate an 'acute abdomen' and lead to referral to a surgeon
- vomiting may be misdiagnosed as gastroenteritis or sepsis
- polyuria and enuresis may be misdiagnosed as a urinary tract infection
- polydipsia may be thought to be psychogenic.

To avoid delay in diagnosis, physicians need to take due care in their detection of diabetes in a patient and in defining its clinical sub-type, since delayed diagnosis of type 1 diabetes in a child or adolescent is associated with an increased risk of DKA (Craig et al 2009b).

At the other end of the clinical presentation spectrum, milder degrees of metabolic decompensation can make it difficult to differentiate type 1 diabetes from type 2 and other forms of diabetes. In such cases, the absence or presence of signs of insulin resistance will help to clarify the diagnosis, including acanthosis nigrans and overweight or obesity; investigations for the detection of islet antibodies including anti-GAD, IAA, ICA, and ZnT-8, as well as a family history of type 1 diabetes, and the clinical course after diagnosis, will also help to differentiate type 1 from type 2 diabetes (Leslie et al 2008).

3.6 Acute complications

Acute complications of diabetes occur to some degree in most people with type 1 diabetes. The complication most feared by people with type 1 diabetes is hypoglycaemia (Anderbro et al 2010; Barnard et al 2010), which is addressed in Chapter 16. Mild hypoglycaemia occurs about twice a week on average in those on an intensive insulin regimen and with a glycated haemoglobin (HbA_{1c}) level of about 7% (DCCT Research Group 1993). Severe hypoglycaemia (in which a person requires assistance from someone else to deal with their episodes of hypoglycaemia) is much less common, occurring, on average about once every 5 person years (DCCT Research Group 1993; Jones and Davis 2003; Cryer et al 2009). However, episodes of severe hypoglycaemia tend to be more frequent in certain people (Cryer 2010; Ly et al 2011), particularly those with :

- a history of severe hypoglycaemia (especially over recent months)
- reduced hypoglycaemia awareness
- a lower HbA_{1c} level
- longer duration of diabetes.

3.6.1 Reduced hypoglycaemia awareness

A major challenge in care of people with type 1 diabetes is reduced hypoglycaemia awareness, where symptoms of hypoglycaemia change and usually become more subtle. This change is associated with the development of autonomic neuropathy, and a reduction in the counter-regulatory response to hypoglycaemia (Ly et al 2011). The condition becomes more common over time, especially after 10 or more years of the disease (Cryer 2010). Some series indicate about 25% prevalence of reduced symptomatic awareness in people with type 1 diabetes, including both children and adults (Jones and Davis 2003; Smith et al 2009). Reduced hypoglycaemia awareness requires increased vigilance in blood glucose monitoring and self-care to prevent severe hypoglycaemia. In some people, reduced hypoglycaemia awareness may improve with avoidance of hypoglycaemia (Ly et al 2011); this topic is addressed in Chapter 16. While adherence to therapy can be difficult to define clinically there is evidence that people with type 1 diabetes who objectively adhere less well to planned therapy regimens have a higher rate of reduced hypoglycaemia awareness (Jones and Davis 2003; Smith et al 2009).

3.6.2 Diabetic ketoacidosis

DKA is life-threatening acute complication of type 1 diabetes. It occurs when insulin delivery is insufficient to prevent progressive hyperglycaemia and ketone body formation. Like hypoglycaemia, DKA can occur in anyone with type 1 diabetes, but is more common when there is a precipitant (e.g. infection of the gastrointestinal, respiratory or urinary tract). DKA also occurs more frequently in people with a past history of DKA, or who adhere suboptimally to self-administration of insulin or care of their diabetes (Skinner 2002). Chapter 17 (on acute complications of diabetes) notes that aiding self-care, adherence to therapy and 'sick day' management can prevent many cases of threatened or mild DKA from worsening and requiring hospitalisation.

3.7 Chronic complications

As with acute complications in type 1 diabetes, chronic complications vary among people and over time in the same person – from subclinical and mild, to end-stage complications. Type 1 diabetes causes both microvascular complications (e.g. retinopathy, nephropathy and neuropathy) and macrovascular complications (e.g. coronary artery disease, peripheral vascular disease and cerebrovascular disease).

3.7.1 Microvascular complications

The development and progression of microvascular complications of diabetes depend strongly on the duration of diabetes (Donaghue et al 2009), and on genetic susceptibility, especially in relation to diabetic retinopathy and nephropathy (Ayodele et al 2004; Wiltshire et al 2008; Wang et al 2010). Nonproliferative diabetic retinopathy eventually occurs in most people with type 1 diabetes (Roy et al 2004; Melendez-Ramirez et al 2010), whereas vision-threatening proliferative retinopathy or maculopathy occurs in a minority (Roy et al 2004).

Subclinical diabetic nephropathy as microalbuminuria occurs in up to 20% of children and adolescents with type 1 diabetes (Mohsin et al 2005; Bogdanovic 2008), and in up to 50% of adults after about 20 or more years of diabetes (Nathan et al 2005). In addition, after 20 years of diabetes, overt nephropathy with macroalbuminuria and proteinuria with reduced glomerular filtration occurs in about 20%, and about one-fifth of these patients progress to end-stage renal disease (Ayodele et al 2004).

Diabetic peripheral neuropathy occurs to some degree in up to 50% of those with type 1 diabetes (Mohsin et al 2005); in a minority of people, it leads to some form of amputation. Autonomic neuropathy (AN), especially cardiac autonomic neuropathy (Rolim et al 2008), is under-recognised; AN contributes to diabetic gastroparesis (Chang et al), cardiovascular disease (Rolim et al 2008) and erectile dysfunction in men (Vinik et al 2003).

3.7.2 Macrovascular complications

Cardiovascular disease – a macrovascular complication – is the main cause of premature death in people with type 1 diabetes of 20 or more years' duration (Secrest et al 2010a). Other macrovascular complications are cerebrovascular and peripheral vascular disease. Some recent data also suggest that the rate of death from type 1 diabetes may be decreasing, compared with previous decades (Nishmura et al 2001; Secrest et al 2010a); this is likely to be associated with more intensive management of risk factors for diabetic nephropathy and cardiovascular disease (Secrest et al 2010a). Macrovascular and microvascular complications of diabetes are each addressed in Chapter 18.

3.7.3 Weight

A significant proportion of people with type 1 diabetes are or become overweight or obese (Purnell et al 1998; Clarke et al 2006; Wei et al 2006; McGill et al 2008). This may in part reflect the increased prevalence of overweight and obesity in the general population. While it is not uncommon for individuals to gain some body weight with intensive insulin therapy (DCCT Research Group 1993; Conway et al 2010) limited data suggest that, in certain cases, intensive treatment of type 1 diabetes may exacerbate overweight, obesity and insulin resistance (Anonymous 1995a; Wei et al 2006). Recent Australian and international studies indicate that the clinical combination of type 1 diabetes and the 'metabolic syndrome' portends a worse prognosis than type 1 diabetes alone (Pambianco et al 2007; McGill et al 2008). Other recent studies have reported that improved glycaemic control through intensive treatment can occur without gain especially if insulin doses can be better matched to insulin requirements (Brown et al 2011).

3.8 Prevention of complications

Clinical trial data indicate that intensive control of blood glucose can slow the natural history of microvascular complications (DCCT Research Group 1993) and – to some extent – macrovascular complications of diabetes (Nathan et al 2009). However, intensive blood glucose control needs to be balanced against the concerns of inducing hypoglycaemia (especially severe episodes), and maintaining quality of life and psychological wellbeing. The management sections of this document focus on individualising care in a person with type 1 diabetes to achieve this balance, optimising the prognosis of the disease (Nathan et al 2009). As described in Chapter 18, secondary prevention, including routinely screening for and detecting key microvascular and macrovascular complications, is also justified (Australian Diabetes Society 2008; Anderbro et al 2010).

4 Impact of type 1 diabetes on the individual and society

The impact of type 1 diabetes on psychosocial functioning, particularly among young people, is widely recognised. Evidence from epidemiological studies suggests that psychological difficulties are more common in children and adolescents with diabetes, as well as in those with other chronic medical conditions (Barlow and Ellard 2006). However, whether people of all ages with type 1 diabetes are at greater risk of psychosocial morbidity and mental health disorders is unclear. This systematic review examined the prevalence of psychological disorders including depression, anxiety and eating disorders across the lifespan of people with type 1 diabetes, compared with the nondiabetic population where controlled data were available.

4.1 Psychological health in type 1 diabetes

Question 4.1

Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?

The detailed systematic review of this question is in Chapter 4 of the accompanying technical report, and the evidence matrix is in Section C4 of Appendix C

4.1.1 Psychological distress

The systematic review identified one study from the United States that estimated the prevalence of severe psychological distress (SPD) among adults with and without diagnosed diabetes (Li et al 2009). The investigators used the Kessler-6 scale, which provides a brief valid screen for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV disorders (Kessler et al 2010). Among 713 adults with type 1 diabetes, the prevalence of SPD was 11%, compared with 3.6% among individuals without diabetes. Significant correlates of SPD among those with diabetes were young age, low education levels, low household income, obesity, current smoking, no leisure-time physical activity, presence of one or more microvascular or macrovascular complications, and disability, suggesting that these factors may contribute to the increased prevalence of SPD in diabetes.

4.1.2 Psychological adjustment, wellbeing and functioning

The systematic review identified four studies that examined the outcomes of psychological adjustment, wellbeing and functioning in children and adolescents (Wake et al 2000; Helgeson et al 2007; Nardi et al 2008; Northam et al 2010).

In a cross-sectional survey of parent and adolescent-reported functional health status, using the Child Health Questionnaire by Wake et al (2000), parents reported that children aged 5–18 years with diabetes had poorer health than children in the normative sample across all domains, particularly on psychosocial and parent/family scales. Psychosocial wellbeing was markedly lower in those aged 5–11 years with HbA_{1c} above 8.8%, but not in those aged 12–18 years. Parents and clinicians concurred in their ratings of health for those aged 12–18 years but not for those aged 5–11 years, suggesting that clinicians may underrate the impact of diabetes for younger children.

The prospective cohort study by Helgeson et al (2007) compared adolescents with diabetes (n=132) with a healthy comparison group (n=131) on indices of psychosocial functioning annually for 3 years. There were no group differences in depressive symptoms, anxiety, anger or behavioural problems. However, adolescents with diabetes showed greater declines in social acceptance compared with healthy adolescents, and a greater rise in disturbed eating behaviour. Among females in both groups, depressive symptoms and anxiety increased, and self-worth decreased over time.

The cross-sectional study of 90 young people with type 1 diabetes (Nardi et al 2008) evaluated self and parent reports of quality of life (QoL) and psychological adjustment compared with controls. There was no difference in psychological adjustment between young people with diabetes and controls. However, parents of children with type 1 diabetes were more worried than those of controls, and adolescents had worse QoL and more frequent psychological problems than controls. HbA_{1c} levels correlated positively with psychological problems (p<0.05) and negatively with QoL (p<0.05).

The 12-year prospective cohort study by Northam et al (2010) compared functional outcomes in 110 adolescents and young adults with type 1 diabetes, compared to 76 community controls, recruited between 1990 and 1992. Follow-up measures of psychosocial wellbeing were the Youth Self Report and Young Adult Self-Report, which provide scores for internalising (anxiety, withdrawal and somatic concerns) and externalising (aggression and delinquency) problems, and a semistructured interview of functional outcomes. While both cases and controls reported similar levels of current psychosocial wellbeing, people with type 1 diabetes were significantly more likely than controls to have had contact with mental health services (37% vs 18%) at some point since diagnosis. Psychiatric morbidity was associated with poor glycaemic control and failure to transition to tertiary adult diabetes care. There was significant correlation between mental health service use and established functional outcome measures, such as lower school completion rates.

4.1.3 Psychiatric disorders

Two studies reported psychiatric status based on a DSM-IV diagnosis (Kovacs et al 1997; Northam et al 2005). In a prospective cohort study of Victorian adolescents, Northam et al (2005) found that 15 out of 41 (37%) received a DSM-IV diagnosis, including mood, anxiety, eating and behaviour disorders. Of those who received a diagnosis, 60% met criteria for two or more psychiatric disorders. Although the study was not controlled, this was two to three times higher than concurrent community levels.

The uncontrolled study by Kovacs et al (1997) found 15/92 children (16%) had a psychiatric disorder at diabetes diagnosis, which predated diabetes onset, while 32% had an adjustment disorder within 3 months of diabetes onset. After 9 years of follow-up, 42% developed at least one episode of psychiatric disorder. The prevalence of major depression was higher than rates in similarly aged cohorts in the general population, and the rate of generalised anxiety disorder (10%) appeared to be higher than the general population rate. An earlier psychiatric disorder increased the risk of later disorder. Initial maternal psychopathology increased the risk of a psychiatric disorder in the young person with type 1 diabetes.

Depression

In an uncontrolled study from the United States, the 26% prevalence of major depression among children, adolescents and young adults was higher than in the general population (Kovacs et al 1997). Maternal depression was a specific risk factor for depression in the participants.

The prevalence of depression among adults with type 1 diabetes was not significantly different from that of the matched control groups in a meta-analysis by Barnard et al (2006) (weighted odds ratio [OR] 2.4, 95% confidence interval [CI]: -0.7 to 5.4). However, only one of the four included studies was considered to be of adequate methodological rigour (Petra et al 2003), and in this study there was a significantly higher rate of major depressive episodes in women with diabetes (9.3% in the diabetes group compared with 3.2% in the reference group), but not in men (3.6% type 1 diabetes compared with 2.2% control). Since the study only included cases of newly diagnosed diabetes, the findings may not be generalisable to the wider population of longer-term patients. The only primary study published since that date that fulfilled the inclusion criteria reported a significantly increased prevalence of depression, based on the Beck Depression Inventory II (BDI-II), in German adults with type 1 diabetes (mean age 44 years, mean duration 29 years) compared to controls (32% vs 16%) (Gendelman et al 2009). Patients with diabetes also reported using more antidepressant medications.

Anxiety

In a prospective study by Kovacs et al (1997), 20% of young people with type 1 diabetes developed some type of anxiety disorder – most commonly generalised anxiety disorder (12%), only diagnosable with DSM-III after age 18, or an overanxious disorder of childhood (8%). The study was not controlled, but the rate of generalised anxiety disorder appeared to be elevated compared to the general population. In the prospective study by Northam et al (Northam et al 2005), 17% of participants received a DSM-IV diagnosis of anxiety 10 years after disease onset.

An uncontrolled, cross-sectional, multicentre study of 276 adolescents examined the prevalence of anxiety symptoms (rather than a diagnosis of anxiety disorder) using the State-Trait Anxiety Inventory questionnaire (Herzer and Hood 2010). The prevalence of trait anxiety symptoms (17%) and state anxiety symptoms (13%) were comparable to published norms for otherwise healthy children. State anxiety symptoms were associated with less frequent blood glucose monitoring and suboptimal glycaemic control.

A systematic review of the prevalence of clinically significant anxiety in adults with diabetes (Grigsby et al 2002) found two controlled studies, but only one of these examined the prevalence of anxiety disorder (Friedman et al 1998). This study from France reported less anxiety and fewer affective disorders, based on self-report measures, in 69 young adults with type 1 diabetes compared to medical outpatients; however, the lifetime prevalence of generalised anxiety disorder was higher than that reported for the general French population. There was also a high lifetime prevalence of not otherwise specified anxiety disorders (44%), simple phobia (27%), social phobia (25%), and agoraphobia – with and without panic disorder (15%), based on DSM-III-R criteria. Current social phobia, dysthymia and not otherwise specified depressive disorders were associated with impaired glycaemic control.

Eating disorders

Two systematic reviews and meta-analyses on eating disorders met the inclusion criteria; both only included studies involving females. Bulimia nervosa was significantly more common in females with type 1 diabetes (1.7%) compared to controls (0.7%) (Mannucci et al 2005). In the earlier meta-analysis (Nielsen 2002), the OR for bulimia was about 3, while both eating disorders not otherwise specified and subthreshold eating disorders were also increased (OR about 2). In contrast, there was no significant difference in the prevalence of anorexia nervosa in adolescent and adult females with type 1 diabetes compared with

controls (Nielsen 2002; Mannucci et al 2005). The cross-sectional study by Ackard et al (2008) found no difference in the rate of eating disorders in adolescent males and females with type 1 diabetes compared with controls.

4.1.4 Summary

Meta-analyses reported no difference in the prevalence of depression in adults with type 1 diabetes compared with the nondiabetic population; however, the methodological quality of three of the four included studies in the systematic review on depression was poor. Two primary studies demonstrated a higher prevalence of depression in adults with type 1 diabetes, at onset of diabetes (Petrak et al 2003) and with long-standing diabetes (Gendelman et al 2009). Evidence from one controlled study in adults showed that the lifetime prevalence of generalised anxiety disorder was higher than that reported for the general population, but there was no difference in the prevalence of anxiety and affective disorders based on self-report measures. Pooled analysis showed an increased prevalence of bulimia nervosa, eating disorders not otherwise specified and subthreshold eating disorders in adolescents and adults with diabetes compared with controls, but no difference in the prevalence of anorexia nervosa.

Controlled studies reported that adolescents and young adults with type 1 diabetes were more likely than controls to have had contact with mental health services, and had higher rates of referral to mental health services (Northam et al 2010). Primary uncontrolled data demonstrated a 26% prevalence of major depressive disorder and 20% prevalence of anxiety disorder in young people with type 1 diabetes (Kovacs et al 1997). Uncontrolled studies showed that 37% of adolescents met criteria for a DSM-IV psychiatric disorder based on a self-report measure (Northam et al 2005) (two to three times higher than community levels); among these, 60% met criteria for two or more psychiatric disorders. Primary studies examining prevalence of eating disorders in young people reported no significant difference between those with diabetes and control groups regarding the incidence of anorexia nervosa. However, binge eating, intense excessive exercise for weight control, reporting two or more current disturbed eating behaviours, and eating disorders not otherwise specified or subthreshold eating disorders were all significantly more common among girls with diabetes than in their peers without diabetes (Colton et al 2007).

The generalisability of these data may be limited by the varied selection and inclusion criteria, as well as the variability in control group selection. The lack of a control group in some paediatric studies may influence the interpretation of the findings. The studies were mostly conducted in Australia, Europe or North America; therefore, the results are applicable to the Australian population.

Evidence statements	
Q4.1	<p>Level I evidence shows that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups – women and the newly diagnosed – than in the general population.</p> <p>Level I evidence shows that there is increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes compared to the general population.</p> <p>Level II evidence indicates that there are higher referral rates to mental health services in children and young adults with type 1 diabetes, compared with the general population.</p> <p>Level IV evidence shows an increased prevalence of depression and anxiety in young people and adolescents with type 1 diabetes, compared with the general population.</p> <p>Level IV evidence shows that the prevalence of anxiety in adults with type 1 diabetes is high, but similar to that in the general population.</p>
Recommendation	
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).
Practice points	
PP4.1.1	Consider the co-occurrence of psychological disorders, including clinical and subthreshold eating disorders, when assessing people with type 1 diabetes and suboptimal glycaemic control, insulin omission, disordered eating behaviours, unexplained weight loss or recurrent DKA admissions.
PP4.1.2	In young people with diabetes, psychological disorders are relatively common compared with prevalence rates for end-organ complications.
PP4.1.3	The diabetes team should assess family functioning (including parental psychopathology) and diabetes-related functioning, including communication, parental involvement and support, roles and responsibilities for self-care behaviours.
PP4.1.4	Validated screening tools for psychological disorders in type 1 diabetes are available.

4.2 What is the impact of type 1 diabetes on cognitive performance?

Question 4.2

What is the impact of type 1 diabetes on cognitive performance?

The detailed systematic review of this question is in Chapter 4 of the accompanying technical report, and the evidence matrix is in Section C4 of Appendix C

People with type 1 diabetes are at risk of developing cognitive difficulties; however, results are inconsistent regarding the magnitude and pattern of cognitive difficulties, due to heterogeneity of study sampling and design, the cognitive abilities examined in the studies, and the assessment tools used. Adolescents with type 1 diabetes have poorer functional academic outcomes (e.g. completion of secondary school) than the general population (Dahlquist and Kallen 2007) or controls (Northam et al 2010), suggesting cognitive abilities may be affected by type 1 diabetes.

To address evidence for the impact of type 1 diabetes on cognitive performance, a systematic review was performed to identify Level I and II studies examining measures of cognitive abilities on cognitive performance in children and adults with type 1 diabetes. The review identified two meta-analyses in children and adolescents, and one in adults (Brands et al 2005; Gaudieri et al 2008; Naguib et al 2009), and four Level II (case-control and cohort) studies (DCCT/EDIC Research Group 2007; Musen et al 2008; Kent et al 2009; Northam et al 2009) that met the inclusion criteria.

4.2.1 Children

Of the two meta-analyses in young people, only one is reported here (Gaudieri et al 2008), because Naguib et al (2009) did not add any additional information. In the meta-analysis of 19 studies involving 2144 children (1393 with type 1 diabetes and 751 controls), diabetes was associated with slightly lower overall intelligence. There were small differences compared with controls across a broad range of specific domains, excluding learning and memory, where performance was similar for those with diabetes and controls. Greater effects on verbal and visual learning and memory were observed in children with early onset diabetes compared to healthy controls and those with late-onset diabetes. A history of seizures was associated with a negligible overall effect on cognition (Gaudieri et al 2008).

Musen et al (2008) examined cognitive performance 18 years later in 249 adolescents aged 13–17 years at entry into the Diabetes Complications and Control Trial (DCCT). The study found no significant effect of treatment assignment or cumulative number of hypoglycaemic events on any cognitive domain. However, higher values of glycated haemoglobin (HbA_{1c}) were associated with modest declines in psychomotor and mental efficiency ($p < 0.01$). A 3 year longitudinal study of young people aged 9–17 years found no significant effect of glycaemic control on verbal memory, but the predicted effect of metabolic control on visual memory using growth curve modelling was significant ($p < 0.01$) (Kent et al 2009). There were no effects of disease duration, age of onset, or severe hypoglycaemia on visual or verbal memory. In the Australian longitudinal cohort study of 106 young people with type 1 diabetes, verbal and full-scale intelligence quotient (IQ) (Northam et al 2009) and working memory (Lin et al. 2010) were significantly lower 12 years after diabetes diagnosis compared with controls (Northam et al 2009). A history of severe hypoglycaemia was predictive of lower verbal IQ (VIQ), and early onset of diabetes predicted lower performance IQ (PIQ). Magnetic resonance spectroscopy and imaging suggested several neuropathological processes including gliosis, demyelination and altered osmolarity might explain the neurocognitive changes observed. The findings from this study contrast with those of an Australian case–control study, which found that episodes of seizure or coma (even those occurring in very early childhood) did not result in broad cognitive dysfunction or specific memory difficulties in children and adolescents with early onset type 1 diabetes compared with their peers (Strudwick et al 2005).

None of the included studies in children examined the effect of hyperglycaemia on cognitive function. However, a crossover study of experimental hyperglycaemia in 12 children demonstrated that acute hyperglycaemia impaired complex cognitive function (Davis et al 1996). In the prospective cohort study of young people in Victoria with type 1 diabetes, those with type 1 diabetes performed more poorly than controls on working memory, and poorer working memory was significantly associated with hyperglycaemia (Lin et al 2010).

4.2.2 Adults

The systematic review of 33 studies of adults with type 1 diabetes demonstrated significantly lower performance on six cognitive domains (intelligence, speed of information processing, psychomotor efficiency, visual and sustained attention, cognitive flexibility and visual perception) compared with controls. While learning and memory appeared to be spared, the authors concluded that even mild forms of cognitive dysfunction had the potential to affect everyday activities. Lower cognitive performance in patients with diabetes appeared to be associated with the presence of microvascular complications, but not with severe hypoglycaemia or with poor glycaemic control (Brands et al 2005).

In the DCCT and EDIC studies, neither treatment assignment nor frequency of severe hypoglycaemia were associated with a decline in any cognitive domain. Higher HbA_{1c} values were significantly associated with moderate declines in motor speed ($p=0.001$) and psychomotor efficiency ($p<0.001$) (DCCT/EDIC Research Group 2007).

4.2.3 Summary

This systematic review of evidence for the impact of type 1 diabetes on the cognitive function of children, adolescents and adults is based on three Level II studies (two of low risk of bias and one of moderate risk of bias), and two meta-analyses at high risk of bias. Most of the studies included in the meta-analyses were of cross-sectional design, making casual inferences problematic. When compared with healthy controls, children and adolescents demonstrated marginal negative effects on several cognitive domains, excluding learning and memory, and scored marginally lower on IQ. Cognitive effects were most pronounced and pervasive for children with early onset diabetes, with moderately lower performance compared with controls. Adults demonstrated a small-to-moderate negative impact on several cognitive domains, excluding learning and memory.

Where the association between occurrence of severe hypoglycaemia and its impact on cognitive function was examined, a significant negative effect was reported in one prospective cohort of children, with severe hypoglycaemia predicting lower VIQ. No other significant effects were reported. Where the association between glycaemic control and impact on cognitive function was examined, significant negative effects were reported in one prospective cohort including adults and adolescents, and in one prospective cohort including children older than 9 years. No significant effects on IQ were reported in one prospective cohort of Australian children, and no significant effects were reported in a qualitative analysis of studies included in a meta-analysis in adults. Early onset diabetes was associated with lower performance and full-scale IQ, verbal and visual learning and memory skills, and attention or executive function skills.

One study was performed in Australia, and the remainder in countries with a well-developed health-care system. Thus, the findings are appropriate to the Australian health-care context. Appropriate exclusions were reported in the studies, including diabetes complications, history of head injury and depression. The absence of clear and consistent associations across the studies may reflect methodological limitations in measuring hypoglycaemia and hyperglycaemia accurately, rather than an absence of association.

Evidence statement	
Q4.2	Evidence from Level I and II studies show a longitudinal association between glycaemic control and some aspects of cognitive function. The magnitude of this effect is greatest in children with early onset type 1
Recommendation	
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).
Practice points	
PP4.2.1	It is important to monitor the school performance of children who developed diabetes before age 5–7 years, and those with a history of significant hypoglycaemic episodes or chronic poor blood glucose control.
PP4.2.2	Early age of onset of type 1 diabetes is associated with a minor but statistically significant reduction in IQ. Therefore, children experiencing significant learning difficulties should be referred for psycho-educational or neuropsychological evaluation. If learning disabilities are present, alternative causes should be sought and remedial interventions to address specific deficits implemented.
IQ, intelligence quotient; QoL, quality of life	

4.3 The impact of type 1 diabetes on growth and physical development

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative contains information from contemporary evidence based guidelines developed by the National Institute of Clinical Excellence (NICE 2010) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Kordonouri et al 2009). The grades of evidence used in these guidelines are shown in Chapter 2, Section 2.2.3 (Tables 2.2 to 2.4).

Among the primary goals of diabetes management in children and adolescents are the maintenance of normal growth, physical and pubertal development, and ideal body weight. In general, children and young people with optimal blood glucose control will grow and develop normally. In an Australian study of adolescents with type 1 diabetes, growth hormone secretion paralleled that seen in normal adolescents during puberty, and growth hormone secretion was not affected by glycaemic control (Batch and Werther 1992). The NICE guidelines found no randomised controlled trials (RCTs) that investigated growth and puberty among children and young people with type 1 diabetes (NICE 2010). Data from cross-sectional and cohort studies of growth in young people with type 1 diabetes are described below.

A number of studies demonstrating a negative impact of type 1 diabetes on linear growth included patients diagnosed more than 20 years ago, at a time when glycaemic targets were higher and the use of intensive management was less common in young people. In a cohort study of 152 children with type 1 diabetes, a linear relationship between HbA_{1c} and growth rate was observed, and patients with total HbA_{1c} above 16% had the greatest growth deceleration (Wise et al 1992). Several groups have reported a reduction in height standard deviation score (SDS) after diagnosis of type 1 diabetes (Bognetti et al 1998; Gunczler and Lanes 1999; Donaghue et al 2003), and a relationship between loss of height and suboptimal glycaemic control (Gunczler and Lanes 1999; Donaghue et al 2003). In a longitudinal study from Germany, growth reduction was more pronounced in patients diagnosed before the onset of puberty, and final height was significantly lower in patients with prepubertal onset of diabetes compared with later onset (Holl et al 1998). There was a greater loss of height in patients with suboptimal glycaemic control. In a smaller Australian study, the mean near-final height Z score was significantly lower than the mean prepubertal height Z score in boys with type 1 diabetes, but not in girls (Kanumakala et al 2002).

Obesity appears to be an emerging problem in young people with type 1 diabetes, particularly among children with young onset of diabetes (<5 years of age) and females (Libman et al 2003; Kordonouri and Hartmann 2005; Clarke et al 2006). Several studies in Australia and overseas have shown that rapid growth and weight gain precede the onset of type 1 diabetes, and children are taller than their peers at diagnosis (Clarke et al 2006), while overweight and obesity persist after diagnosis, particularly in older children. It is thought that overweight in early childhood may initiate islet autoimmunity (Couper et al 2009) and accelerate beta cell loss (Wilkin 2001). This contrasts with the weight loss that occurs in the weeks or months before diagnosis due to hyperglycaemia. Factors contributing to overweight in type 1 diabetes include the requirement for supraphysiological insulin doses to achieve glycaemic targets, excess energy from inappropriate snacks, and excess energy intake to avoid or treat hypoglycaemia. Obesity is an independent risk factor for macrovascular disease in type 1 diabetes (discussed in Chapter 18). Obesity is also a risk factor for microalbuminuria in adolescents with type 1 diabetes (Stone et al 2006).

Summary

The measurement of height, weight and body mass index is an integral component of diabetes care for children and adolescents. It is preferable for height and weight to be measured in a private room (NICE 2010). Plotting of anthropometric measurements on an appropriate centile chart is an integral component of diabetes care for children and adolescents. Changes in growth or significant changes in weight, or pubertal delay, may reflect changing glycaemic control. In such cases, comorbidities such as coeliac disease or thyroid dysfunction should also be considered.

Dietary advice and meal planning should be revised regularly to meet changes in appetite and insulin regimens, and to ensure optimal growth. Prevention of overweight and obesity is a key strategy in the management of type 1 diabetes (see Chapter 10).

Regular review and adjustment of insulin doses (and basal rates on pumps) are required in children and adolescents, because insulin requirements can change rapidly with growth and puberty. In particular, significant insulin resistance may occur during puberty, and insulin requirements typically increase (>1 unit/kg/day). Postpubertally, insulin doses usually decline.

4.4 Urban versus rural care of type 1 diabetes in Australia

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative provides background information only; no evidence-based guidelines are referenced in this section.

Multidisciplinary teams (as defined in Section 8.1), are not available in many rural and geographically remote areas of Australia that have low population density and small numbers of people with type 1 diabetes, particularly children. In these situations, care may be provided by a local paediatrician or physician with access to resources, support and advice from a tertiary centre diabetes team. It is not known whether a lack of multidisciplinary team care, or other factors related to living rural locations, influence glycaemic control. A systematic review was not performed for this question, because no RCTs examining the effect of interventions on glycaemic control in urban versus rural patients were identified. Three cross-sectional studies that examined glycaemic control in young people with type 1 diabetes living in rural areas were identified (Handelsman et al 2001; Cameron et al 2002; Goss et al 2010). One of these studies included a control group of urban youth (Cameron et al 2002).

The largest study was an audit of about 1200 children with type 1 diabetes living in New South Wales and the Australia Capital Territory, in which glycaemic control did not differ between those from urban and those from rural areas (Handelsman et al 2001). A Victorian study on clinical and QoL outcomes demonstrated no differences in glycaemic control between youth with type 1 diabetes living in urban and rural locations, despite less reported access to team-based diabetes care in rural centres (Cameron et al 2002). However, rural youth had lower QoL and the greatest deficits were seen in areas of mental health, self-esteem, parent impact (emotional) and family cohesion. Following implementation of a multidisciplinary paediatric diabetes clinic in rural Victoria, glycaemic control improved significantly from a median of 9.7% to 7.9%. Although there was no urban comparison group, the level of glycaemic control was comparable with that achieved in patients managed in urban centres (Goss et al 2010). There are limited data regarding glycaemic control in adults with type 1 diabetes from regional areas. In an audit of 239 young adults (aged 18-28 years) with type 1 diabetes from New South Wales, median HbA1c was

significantly higher for those from regional centres in the first year following transition to adult care (9.4%), compared with those attending a young adult diabetes clinic in Sydney (8.4%) or Newcastle (a regional city, 8.7%). Routine uptake of diabetes care during the first year of contact with adult services was significantly higher in Sydney and Newcastle compared with the regional areas (Perry et al 2010).

These findings suggest that the glycaemic control of young people with type 1 diabetes is not influenced by location of residence. Thus, care provided locally in urban centres, or in partnership with outreach services, is likely to be comparable to that in regional centres for young people with type 1 diabetes. However, there is some evidence for lower QoL in rural youth. In contrast, one study of young adults showed worse glycaemic control following transition in those from regional areas of NSW (Perry et al 2010). The management of patients living in rural and remote areas using telemedicine is covered in Chapter 8.

Summary

All people with type 1 diabetes, including those from rural and remote areas, should have access to optimal medical management. In rural and geographically remote areas within the Australian health-care system, people with diabetes may be successfully cared for by a local paediatrician or physician, and a multidisciplinary health-care team experienced in diabetes, with access to resources, support and advice from a tertiary centre diabetes team.

4.5 The cost burden of type 1 diabetes to individuals and society

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative is based on a recent Australian review of the cost of type 1 diabetes in Australia (Colagiuri et al 2009) and also contains information from evidence based guidelines developed by the National Institute of Clinical Excellence (NICE 2010). The grading of evidence used in the NICE guidelines is shown in Chapter 2, Section 2.2.3 (Tables 2.3 and 2.4).

A recent review (DiabCo\$T Type 1) was identified that described the cost of type 1 diabetes in direct health-system costs, indirect costs and QoL (Colagiuri et al 2009). DiabCo\$T Type 1 was a retrospective, cross-sectional, self-reported survey of people with type 1 diabetes, aged 5 years and older, in Australia. Participants were randomly selected from the National Diabetes Services Scheme (NDSS) register, with appropriate permission and compliance with privacy regulations. A stratified random sample of 10 000 people was sent a survey in August 2006. Parents, guardians or carers were asked to assist with completing the survey when it was sent to children. The respondents were anonymous to both the study investigators and the administrators of the NDSS. The survey comprised two structured, self-administered questionnaires, one for people with diabetes and another for their carers. The questionnaires were designed to elicit information on costs incurred over the previous 3 months. In addition, QoL for people with type 1 diabetes was assessed using the EuroQuol (EQ-5D), an instrument for measuring health-related quality of life states that consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

The DiabCo\$T Type 1 survey collected direct health-care costs, non-health care costs and indirect costs for people with type 1 diabetes, costs to carers, and an assessment of the impact of type 1 diabetes on the individual's QoL. The survey measured total health costs for the study respondents. It was not intended or possible to separate health-care costs attributable to diabetes and those incurred for non-diabetes related conditions.

The number of evaluable questionnaires returned was 2200 (response rate 22%). The mean age of respondents was 32 years, and time since diagnosis was just over 8 years. Most participants (82.7%) reported no complications. Microvascular complications alone were reported by 12.3%, macrovascular complications alone by 0.7%, and both microvascular and macrovascular complications by 4.3%. Mild hypoglycaemic episodes in the 3 months preceding the survey were reported by 88.7%, with a mean number of just under 16 episodes within that 3-month period. About 19% reported experiencing a mean of almost three severe hypoglycaemic episodes requiring assistance. About one-third of respondents reported having a carer. The mean age of carers was 42.9 years, and 90% were female (Colagiuri et al 2009).

The total average annual cost per person with type 1 diabetes was \$4669. This figure comprised \$3862 in direct costs (\$3640 direct health costs and \$222 direct non-health costs) and \$807 in indirect costs (\$418 related to the person with type 1 diabetes and \$389 related to carer costs). Hospitalisation accounted for nearly half of the direct health-care costs. Medications accounted for 32%, with insulin accounting for about 14%. Ambulatory service costs were derived from visits to general practitioners (3.7%), medical specialists (7.7%) and allied health professionals (4.8%) such as diabetes educators, dieticians or nutritionists, podiatrists, psychologists and optometrists. Consumables, blood glucose testing strips and insulin-administering equipment accounted for 4.5% of direct health-care costs (Colagiuri et al 2009).

Costs increased with the presence of complications. The average total annual cost was \$3468 for people without complications, \$8122 for people with microvascular complications only, \$12 105 for people with macrovascular complications only, and \$16 698 for people with both macrovascular and microvascular complications.

Nineteen percent of carers reported being retired or currently not working in order to care for the person with diabetes. Carers took an average of almost 3 days off work in the previous 3 months to care for the person with diabetes. The employment situation of 17% of carers had changed to care for the person with diabetes, with an accompanying reduction in income for nearly 70% of these carers, resulting in mean annual lost wages of \$7413 per carer (Colagiuri et al 2009). People with type 1 diabetes reported an impact on health-related QoL, particularly for the 'pain/discomfort' and 'anxiety/depression' dimensions. QoL scores were lower in people with complications.

This was the first individual level assessment of the financial and personal impact of type 1 diabetes on the person with diabetes and their carer in Australia. The minimum estimated cost to the nation of type 1 diabetes ranges from \$430 to \$570 million, depending on the data used to estimate the number of people with type 1 diabetes in Australia. These costs are substantially higher than previous estimates, which were based on administrative rather than patient-level data. The real cost is even higher, since the full impact of indirect costs associated with premature mortality could not be assessed because this was a self-reported questionnaire, and the survey did not evaluate the cost of disability (Colagiuri et al 2009).

These findings have important implications for policy and service delivery for people with type 1 diabetes and their carers. The role of complications as a cost driver underlines the need to ensure access to appropriate standards of care, to prevent or delay the onset of complications.

The cost of type 1 diabetes was also examined in the NICE guidelines (NICE 2010). NICE reviewed the economic analysis of the DCCT, which examined the cost effectiveness of

alternative approaches to the management of type 1 diabetes. An economic simulation model was constructed to estimate the lifetime costs and outcomes of conventional and intensive insulin therapy. Quality-of-life scores assigned to specific health states were not based on primary research into the social valuations for different health states (as would be normally be expected in health economic evaluation). The simulations showed that the mean annual cost of intensive therapy using multiple daily injections was around \$4000, and for continuous subcutaneous insulin infusion (CSII) was \$5800. The figure for CSII is approximately three times the mean annual cost of conventional therapy (which is \$1700). The model estimated that the cost of the adverse effects of intensive therapy was three times the cost of the adverse effects of conventional therapy, but these costs accounted for only about 5% of the total costs of therapy in both groups. The expected lifetime cost per patient was around \$100 000 for intensive therapy and \$66 000 for conventional therapy at 1996 prices. The analysis concluded that intensive therapy cost \$28 661 per year of life gained.

No study has estimated the cost effectiveness of alternative forms of treatment for children and young people. The DCCT model included patients aged 13–39 years, and so the costs and benefits associated with children and young people cannot be estimated from this model. Furthermore, the cost of initiation of intensive therapy was around \$2900. More than 85% of this cost was attributable to hospitalisation to initiate intensive therapy, but this level of hospitalisation might not be expected in health-care settings outside a research environment. Further research based on the experience of children and young people accessing conventional and intensive forms of treatment in routine clinical care is required.

In subsequent chapters, cost-effectiveness studies for interventions addressed in the Recommendations and Practice Points, with a focus on medical therapies, were included where systematic reviews were available for studies conducted in health care systems similar to Australia. A strategy of intensive glycaemic control in people with type 1 diabetes, with characteristics of those included in the DCCT, strongly justified a reduction in long-term complications of diabetes, and over a lifetime, DCCT-defined intensive treatment improved quality of life, and could be expected to extend life span. Insulin analogue therapy was cost effective in the treatment of type 1 diabetes, based on quality-adjusted life years and quality-adjusted life expectancy. CSII approaches could be economically justified in developed countries if the degree of improvement in long term glycaemic control was substantive - such as a more than 0.5% sustained improvement in HbA1c levels; this was predicted to translate into a reduced rate and severity of diabetes end-organ complications. Therapy with ACEI or ARB to prevent end-stage renal disease, compared with no ACEI or ARB treatment, was cost effective in type 1 diabetes.

Cost effectiveness was not systematically reviewed where no level I or level II evidence was found for a systematically reviewed question in this guideline, or a clear definition of the specific intervention or target populations was lacking, or if the topic was not systematically reviewed (e.g. screening tools for psychological disorders in type 1 diabetes; CGMS systems; metformin in type 1 diabetes; nutrition programs; contraception methods; specific transition programs; blood glucose awareness training, sick day blood ketone monitoring compared with urine ketone monitoring; statin therapy and screening for thyroid dysfunction and coeliac disease). In addition, cost-effectiveness studies in specific nutrition or diabetes education programs were not identified during the systematic review process. Finally, while the cost effectiveness of preconception care in type 1 diabetes was not systematically reviewed in this guideline, it has been reported by others to be robustly cost effective (Herman et al 1999) with a benefit to risk ratio of 1.86 (Elixhauser et al 1993).

5 Role of major trials in advancing clinical care in blood glucose management

5.1 Introduction

The information provided in this chapter was not systematically reviewed; the narrative text provides background information on the impact of major trials, including the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, on glycaemic control. The effect of intensive diabetes management on the incidence of severe hypoglycaemia (Chapter 16) and the effect of intensive glycaemic management on microvascular and macrovascular complications (Chapter 18) were systematically reviewed. This chapter also provides information on glycaemic target setting from the International Society for Pediatric and Adolescent Diabetes (ISPAD) evidence based guidelines (Rewers et al 2009). There are no recommendations or practice points made in this chapter; the clinician should refer to these guidelines for further information.

Blood glucose management in type 1 diabetes is important to prevent acute metabolic deterioration, with life-threatening diabetic ketoacidosis (DKA) or severe hypoglycaemia. The great importance of long-term blood glucose control in preventing the development and worsening of diabetes end-organ complications was established by a definitive randomised controlled trial (RCT) – DCCT. The EDIC was a longitudinal, observational study that used the DCCT participant cohort, which confirmed the importance of glycaemic control on microvascular complications and demonstrated effects of glycaemic control on macrovascular outcomes. These two major trials are summarised below.

5.1.1 Diabetes Control and Complications Trial

The DCCT, a multicentre RCT, was designed to compare the effects of intensive versus conventional diabetes therapy on the development and progression of the early vascular and neurological complications of diabetes (DCCT Research Group 1986; DCCT Research Group 1993). Two cohorts were studied, to answer two different questions:

- Will intensive therapy prevent the development of diabetic retinopathy in people with no retinopathy?
- Will intensive therapy affect the progression of early retinopathy?

The primary study outcome was retinopathy. Secondary outcomes were renal, neurologic, cardiovascular and neuropsychological effects, as well as the adverse effects of the two treatment regimens.

The major criteria for eligibility included insulin dependence (as measured by deficient C-peptide secretion); age 13–39 years; and the absence of hypertension, hypercholesterolemia and severe diabetic complications or medical conditions.

Intensive therapy aimed to maintain blood glucose concentrations close to the normal range while preserving clinical wellbeing, as defined for the standard treatment group. The targets were (DCCT Research Group 1993):

- preprandial blood glucose concentrations between 3.9 mmol/L and 6.7 mmol/L
- postprandial concentrations of less than 10 mmol/L
- weekly 3-am measurement of more than 3.6 mmol/L
- glycated haemoglobin (HbA_{1c}) measured monthly within the normal range (<6.05%)
- weekly clinic visits until the target range was reached, and monthly visits thereafter

The intensive therapy methods included the subcutaneous administration of insulin three or more times daily by injection or by an external pump infusing insulin (continuous subcutaneous insulin infusion [CSII]). The dosage was adjusted based on the results of self-monitoring of blood glucose (SMBG), dietary intake and anticipated exercise. SMBG was performed at least four times per day, with at least weekly 3-am measurement. The participants initially chose either multiple daily injection or CSII therapy, and could change to the other method based on personal preference or targets. Participants visited the study centre each month, and were contacted even more frequently by telephone for review and dose adjustment. Telephone contact was maintained at least weekly. The objective of the standard treatment regimen (conventional therapy) was to maintain the clinical wellbeing of the person with type 1 diabetes. Wellbeing was defined as freedom from symptoms attributable to glycosuria or hyperglycaemia; freedom from frequent or severe hypoglycaemia; absence of ketonuria; normal growth and development in adolescents; and maintenance of ideal body weight in all participants. An upper action limit of 13.11% was set for HbA_{1c}; this value mandated therapeutic intervention (DCCT Research Group 1993).

A total of 1441 participants with age range 13–39 years were recruited across 29 centres from 1983 to 1989. The entire cohort was followed for a mean of 6.5 years, which gave more than 9300 person years; 99% of participants completed the study. Eleven participants died and 32 were assigned to inactive status.

At baseline, the mean age was 27±7 (± standard deviation) years in all groups, except for those assigned to conventional therapy in the primary prevention cohort, for whom the mean age was 26±8 years. Most participants were classified as being of ‘white race’ ethnicity. The average duration of diabetes was 2.6±4 years in the primary prevention cohort and 8.6–8.9 years in the secondary intervention cohort. The mean HbA_{1c} was 8.8% in the primary prevention cohort and 8.9–9% in the secondary intervention cohort.

The data safety and quality committee stopped the RCT phase of the DCCT prematurely after a mean follow-up of 6.5 years (DCCT Research Group 1993). The benefits of intensive treatment were deemed incontrovertible, and highly unlikely to be reversed with time. During the closeout period of the study, all participants were encouraged and advised to implement or continue intensive treatment using DCCT staff.

The overall within-participant mean HbA_{1c} levels for the entire DCCT period were 9.1% for the conventional group and 7.2% for the intensive treatment group ($p<0.001$) (Lachin et al 2008). Among those in the intensive group, 50% of participants had a mean HbA_{1c} between 6.5 and 7.5%, compared to 8% of the conventional group. Among those in the conventional group, 31% had a mean HbA_{1c} between 8.5 and 9.5%, compared to 5% of the intensive group (Lachin et al 2008). Forty-four percent of participants receiving intensive therapy achieved the goal HbA_{1c} of 6.05% or less at least once during the study. Less than 5% maintained an average value in this range. The mean value for all glucose profiles in the intensive therapy group was 8.6±1.7 mmol/L. In the conventional group, the mean value was 12.8±3.1 mmol/L ($p<0.001$) (DCCT Research Group 1993).

Microvascular outcomes

In the primary prevention cohort, intensive therapy (where a median HbA_{1c} of 7.3% was achieved) reduced the adjusted mean risk for the development of retinopathy by 76% (95% confidence interval [CI]: 62% to 85%) compared with conventional therapy (median HbA_{1c} of 9.1%) (DCCT Research Group 1993). These data are summarised in Chapter 18 of the technical report. Those in the primary prevention cohort with duration of diabetes of less than 2.5 years at entry into the trial had 89% reduction in the risk of retinopathy, compared with 70% in participants with duration of more than 2.5 years ($p < 0.001$). In the secondary-intervention cohort, intensive therapy slowed progression of retinopathy by 54% (95%CI: 39% to 66%) and reduced the development of proliferative or severe nonproliferative retinopathy by 47% (95%CI: 14% to 67%) (DCCT Research Group 1993).

In the primary prevention cohort, there was an early worsening of retinopathy (DCCT Research Group 1995). This occurred in 22% of participants in the intensive treatment group, compared with 13% in the conventional group (odds ratio [OR] 2.06, $p < 0.001$) (Anonymous 1998a). The progression consisted of the development of soft exudates or intraretinal microvascular abnormalities. This occurred mainly in the secondary intervention cohort, and was most commonly observed during the first year of intensive therapy (DCCT Research Group 1993). The abnormalities often disappeared by 18 months. Participants with early worsening who were treated intensively ultimately had a 74% reduction (95%CI: 46% to 88%) in the risk of subsequent progression, compared with those with early worsening who received conventional therapy ($p < 0.001$) (Anonymous 1998a).

In terms of nephropathy, in combined cohorts, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥ 40 mg per 24 hours) by 39% and albuminuria by 54% (DCCT Research Group 1993). Observational data showed that the risk of developing nephropathy was exponentially related to mean HbA_{1c}; for each 10% decrease in HbA_{1c} there was a 25% decrease in the risk of microalbuminuria (DCCT Research Group 1993). No glycaemic threshold for nephropathy was detected above the nondiabetic range of HbA_{1c}. The DCCT found no influence of intensive treatment on glomerular filtration rate; however, these values remained within normal range for most participants during the DCCT.

Intensive therapy reduced the odds of having symptoms and signs of peripheral neuropathy by 64% ($p = 0.0044$) and 45% ($p < 0.0001$) respectively. In the primary intervention cohort who did not have peripheral neuropathy at baseline, intensive treatment reduced the appearance of clinical peripheral neuropathy at 5 years by 69% (to 3%, compared with 10% in the conventional therapy group, $p < 0.001$). In the secondary intervention cohort, intensive treatment also reduced the appearance of clinical peripheral neuropathy at 5 years, by 57% (7% compared with 16%, $p < 0.001$). Autonomic neuropathy signs were also minimised by intensive compared with conventional therapy, by 53% ($p = 0.04$) (DCCT Research Group 1993). Nerve conduction velocities generally remained stable with intensive therapy, but decreased significantly with conventional therapy (1995c).

Macrovascular outcomes

The DCCT was not powered to assess effects of glycaemic control on macrovascular outcomes; however, intensive therapy was associated with a lower risk of development of macrovascular disease. The number of combined major macrovascular events was almost twice as high in the conventionally treated group (40 events) than in the intensive treatment group (23 events); a difference in rates that was not statistically significant (DCCT Research Group 1993; Anonymous 1995b).

Adverse events

Mortality did not differ significantly between the treatment groups, nor did overall DKA events. There were also no significant differences between groups with regard to the number of major accidents requiring hospitalisation. The incidence of severe hypoglycaemia, including multiple episodes in some participants, was approximately three times higher in the intensive therapy group than in the conventional therapy group ($p < 0.001$), with grade 2 or 3 hypoglycaemia occurring as 62 episodes per 100 person years in the former, and 19 in the conventional group (DCCT Research Group 1993). Most severe episodes occurred at night. Development of hypoglycaemia unawareness was also more common in the intensive treatment group (Lorenz et al 1991). There were two fatal motor vehicle crashes, one in each group, in which hypoglycaemia may have been a factor. In addition, a person not involved in the trial died in a motor vehicle accident involving a car driven by a participant in the intensive group who was probably hypoglycaemic (DCCT Research Group 1993).

Quality of life

Despite the higher risk of severe hypoglycaemia with intensive therapy, there was no difference between the two groups in the occurrence of clinically important changes in neuropsychological function, nor were there any statistically significant differences in the mean total scores in the quality of life (QoL) questionnaire (DCCT Research Group 1993; DCCT Research Group 1996). Thus, by this measure, QoL was maintained in the intensive treatment group, despite an increase in the rigor of diabetes care. During the DCCT, there was a 33% increase in the mean adjusted risk of becoming overweight in the intensive group, compared with a 9.3% increased risk in the conventional group. At 5 years' study duration, participants in the intensive group had gained a mean of 4.6 kg more than those receiving conventional therapy.

5.1.2 Epidemiology of Diabetes Interventions and Complications study

The Epidemiology of Diabetes Interventions and Complications (EDIC) study was a multicentre, longitudinal, observational study that used the DCCT cohort of participants. The aim of the EDIC study was to determine the long-term effects of prior separation of glycaemic levels on multiple microvascular and macrovascular outcomes (Lachin et al 2000; DCCT/EDIC Research Group 2002). Of the 29 DCCT clinics, 28 opted to participate as EDIC clinical centres. Each participant had a standardised annual history and physical examination. The examination included detailed evaluation of overall health status, diabetes management and occurrence of diabetic complications. Measures of health satisfaction and quality of life were obtained every other year. The study outcomes were to:

- describe the development and progression of cardiovascular (coronary, peripheral and cerebral) disease in type 1 diabetes
- study the effects and interactions of potential risk factors for cardiovascular disease in type 1 diabetes
- examine the long-term effects of differences in prior diabetes treatment (conventional vs intensive) during the DCCT on the subsequent development and progression of cardiovascular disease
- examine the development of abnormal lipid and lipoprotein levels
- relate early degrees of microalbuminuria to the development of nephropathy
- study the rate of development of neuropathy
- examine the transition to retinopathy

- examine long-term effects of differences in prior control on microvascular complications
- examine effects of putative genetic factors
- observe current health care, implementation and maintenance of intensive therapy
- study health related to quality of life

At the end of EDIC year 1, 95% of the former intensive therapy group and 75% of the former conventional group reported that they were using intensive treatment. The mean HbA_{1c} levels were 7.9% for the former intensive treatment group and 8.3% in the former conventional group. The HbA_{1c} levels converged further, and remained similar during the ensuing 7 years (DCCT/EDIC Research Group 2002). The overall mean HbA_{1c} levels for the entire EDIC follow-up until 2002 were 8.3% for the former conventional group and 8.1% for the intensive treatment group (DCCT/EDIC Research Group 2002).

Microvascular outcomes

In EDIC, the microvascular outcomes seen at the DCCT closeout were largely maintained (Lachin et al 2000; DCCT/EDIC Research Group 2002). There was a strongly positive exponential relationship between the risk of retinopathy and mean HbA_{1c}, measured quarterly. For each 10% decrease in HbA_{1c}, there was a 39% decrease in risk of retinopathy over the range of HbA_{1c} values. There was no glycaemic threshold at which the risk of retinopathy was eliminated above the nondiabetic range of HbA_{1c} (4.0–6.05%). For each 10% decrease in HbA_{1c} during the DCCT, there was a 25% decrease in the risk of microalbuminuria. In EDIC, after 4 years, the proportion of participants with progressive retinopathy and nephropathy (as albuminuria) was reduced ($p < 0.001$ for each endpoint) in the intensive treatment group of the DCCT compared with the original conventionally treated group. After five years, the prevalence of confirmed clinical neuropathy in those without neuropathy at baseline decreased by 69% in the primary cohort and 57% in the secondary cohort.

In the longer-term EDIC follow-up, the original DCCT intensive treatment also reduced the risks of onset and progression of some endpoints assessing autonomic neuropathy. Specifically, for the original intensive treatment group, incident cardiac autonomic neuropathy was reduced by 31% (OR 0.69, 95%CI: 0.51 to 0.93) and incident abnormal cardiac R-R interval variation by 30% (OR 0.70, 95%CI: 0.51 to 0.96) in EDIC year 13–14, compared with those in the original DCCT conventional therapy group (Pop-Busui et al 2009). In contrast, orthostatic hypotension prevalence did not differ between the two groups and, as in the DCCT, in EDIC a decreased awareness of hypoglycaemia was more common in the original intensive treatment group (DCCT Research Group 1998b). Cognitive outcomes were not different between the two groups in EDIC (Jacobson et al 2007); no evidence of substantial long-term declines in cognitive function was found in participants carefully followed for an average of 18 years, despite relatively high rates of recurrent severe hypoglycaemia. Higher HbA_{1c} values were associated with moderate declines in motor speed ($p = 0.001$) and psychomotor efficiency ($p < 0.001$) (Jacobson et al 2007).

Cardiovascular outcomes

In EDIC, a total of 144 cardiovascular events occurred in 83 participants during the mean 17 years of follow-up; 46 among 31 people in the intensive treatment group and 98 among 52 people in the conventional group. The respective event rates were 0.38 and 0.80 per 100 person years ($p = 0.007$) (Nathan et al 2005). The risk of the first occurrence of nonfatal myocardial infarction, stroke or death from cardiovascular disease (CVD) was reduced by 57% with intensive treatment compared with conventional treatment (96%CI: 12% to 79%,

$p=0.02$) (Nathan et al 2005). The presence of diabetic nephropathy mediated about 50% of the effects of glycaemia on cardiovascular outcomes, and blood glucose accounted for well over 90% of the observed effect (rather than lipid or blood pressure levels and their treatments). A study of the surrogate endpoint of carotid intima-media thickness (CIMT) some years earlier had reported in EDIC that between the intensive therapy and conventional group, there was less progression of the intima-media thickness of the common carotid artery to year 6 of the EDIC in intensive treatment groups (Nathan et al 2003). Mean CIMT progression was 0.032 mm in the intensive treatment group and 0.046 mm in the conventional group, with a difference of 0.013 mm (95%CI: 0.003 to 0.24).

5.2 Across the lifespan

Compared with the adults in the DCCT, the adolescent subgroup ($n=195$, aged 13–17 years) had similar microvascular benefit and similar adverse events in terms of the relative risk of severe hypoglycaemia in intensive and conventional treatment (DCCT Research Group 1994). The benefits did not clearly persist, however, in adolescents who continued into the EDIC (White et al 2010). Nearly 80% of the observed differences in the prolonged treatment effect between adults and adolescents at year 10 of the EDIC were explained by differences in mean HbA_{1c} during the DCCT between adolescents and adults. This finding indicates that tight glycaemic control is required in adolescence to optimise outcomes into adulthood.

The DCCT and EDIC did not study people with advanced end-stage diabetes end-organ complications, and it is not clear whether tight glycaemic control as a strategy will lead to improved outcomes in this cohort. As the benefits of tight glycaemia control persist across decades, the memory effect (explained below) of elevated glucose reinforces the importance of tight glycaemic control as a method to minimise risk of diabetes microvascular and macrovascular complications in the long term.

5.3 Metabolic control matters – putting glycaemic control into context

The DCCT study provides evidence that intensive diabetes treatment and improved glycaemic control confers a significant risk reduction for microvascular complications compared with conventional treatment. The EDIC study has shown that this positive effect continues after randomisation. This phenomenon has been termed ‘metabolic memory’; the long-term effect of hyperglycaemia on the risk of microvascular complications may be mediated by the generation of advanced glycation end products. The EDIC also showed a positive effect of intensive therapy on reduction in macrovascular disease; the beneficial effect of intensive treatment on the risk of CVD may be a result of the reduction in the incidence of microvascular disease. In the EDIC study nephropathy accounted for approximately 50% of the variation in CVD risk (Nathan et al 2005).

More recent studies have confirmed that HbA_{1c} explains virtually all the risk difference in complications between the intensive and conventional groups, and a given HbA_{1c} level has similar effects within the two treatment groups (Lachin et al 2008). Other components of hyperglycaemia, such as glucose variation, may contribute to complications risk, but such factors can only explain a small component of the risk difference between intensive and conventional therapy over time (Lachin et al 2008).

5.4 Glycaemic target setting

5.4.1 HbA1c

The DCCT was not designed to assign participants to multiple treatment levels of glycaemia. Thus, the question of a glycaemic target that would preserve the benefits of intensive therapy but reduce the risk of severe hypoglycaemia could not be directly answered by the study. However, the relationship between the rate of development of retinopathy and glycaemic exposure (HbA_{1c} over time) was analysed. These secondary analyses showed a continuously increasing risk of sustained progression of retinopathy by three steps with increasing mean HbA_{1c}. The risk of severe hypoglycaemia also increased continuously with lower monthly HbA_{1c} values. Thus, the findings did not support the existence of one specific target value for HbA_{1c} that would maximise benefits and minimise risk. The intensive treatment group achieved, on average, an HbA_{1c} level of below 7.2%; hence, a value below this level is generally set as the generic HbA_{1c} target in adults with type 1 diabetes.

In children and adolescents, achieving tight glycaemic control by intensive therapy is more challenging, with a greater risk-to-benefit ratio due to severe hypoglycaemia (Fenton et al 1999). The intensively treated adolescent cohort of the DCCT achieved a mean HbA_{1c} of 8.1%. While evidence from the DCCT is available for adolescents, recommendations for younger children are derived from these data and expert opinion (ISPAD 2009). However, targets for young people should be individually determined, aiming to achieve a value as close to normal as possible while avoiding both severe hypoglycaemia and frequent mild to moderate hypoglycaemia (ISPAD 2009).

In Australia, HbA_{1c} targets in type 1 diabetes are <7.5% for children and adolescents (APEG 2005; Rewers et al 2009) and <7.0% in adults (Cheung et al 2009b), with HbA_{1c} levels being performed every 3 to 4 months.

5.4.2 Blood glucose targets

For adults in the intensively treated group of the DCCT, blood glucose targets were:

- Before meals 3.9 to 6.7 mmol/L
- After meals 5 to 10 mmol/L
- At 3am (weekly) above 3.6 mmol/L

For young people with type 1 diabetes, targets are (Ambler and Cameron 2010):

- Before meals 4 to 7 mmol/L
- After meals 5 to 10 mmol/L
- At bed time 6 to 10 mmol/L
- At 3am 5 to 8 mmol/L

Blood glucose targets may be set higher for infants and young children:

- Before meals 5 to 10 mmol/L
- After meals 6 to 10 mmol/L
- At bed time 6 to 12 mmol/L

It is emphasised that blood glucose targets need to be individualised for each person with type 1 diabetes. Clinical trials targeting intensive blood glucose control such as the DCCT

typically exclude people at highest risk of severe hypoglycaemia, with advanced end-stage diabetes complications, with poor adherence to therapy or with major intercurrent medical conditions (DCCT Research Group 1993). The average duration of diabetes was only 2.6 years at study entry in the intensive treatment arm of the DCCT, for the average 6.5 years' study duration. Thus, the DCCT and EDIC mainly examined the importance of tight glycaemic control in the first 10 years after diabetes diagnosis. In contrast, glycaemic control typically becomes more difficult to achieve safely with increasing diabetes duration of, and both a lack of hypoglycaemia awareness and severe hypoglycaemia become increasingly common.

5.5 Relationship between HbA_{1c} and blood glucose level

There is a close linear relationship between HbA_{1c} and average blood glucose in a clinically relevant range of glycaemia, as shown in Table 5.1 (Nathan et al 2008). While there are well-recognised clinical factors, such as anaemia and altered erythrocyte turnover, which can affect HbA_{1c} results measured using all assay methods, and hemoglobinopathies, which interfere with specific methods for HbA_{1c} measurement (Bry et al 2001), the table below provides a useful index of chronic glycaemia for individuals with type 1 diabetes.

Table 5.1—Estimated average glucose

HbA _{1c} (%)	Blood Glucose Level mmol/L
5	5.4 (4.2–6.7)
6	7.0 (5.5–8.5)
7	8.6 (6.8–10.3)
8	10.2 (8.1–12.1)
9	11.8 (9.4–13.9)
10	13.4 (10.7–15.7)
11	14.9 (12.0–17.5)
12	16.5 (13.3–19.3)

5.6 Measurement of HbA_{1c}

HbA_{1c} provides an indicator of longer-term average blood glucose (e.g. previous 2-3 months) and is considered the best marker of long-term diabetes control. A recent consensus statement on the global standardisation of HbA_{1c} (Hanas and John 2010) updated previous international recommendations on the standardisation and reporting of HbA_{1c}. At present, all HbA_{1c} methods routinely used in Australia are traceable to the International Federation of Clinical Chemistry reference system. This is in place in most countries worldwide. The new recommendation is to report all HbA_{1c} results in SI (Système International) units (mmol/mol, no decimals) as well as the usual derived National Glycohemoglobin Standardization Program units (% , one decimal place). This dual reporting, both as mmol/mol and %, will be maintained for two years before % reporting will be phased out. The key reasons for implementing this recommendation in Australia are as follows (Jones et al 2011):

- The SI units relate to a scientifically valid measure of HbA_{1c}
- The reporting is in keeping with the international consensus document
- The SI units remove potential confusion of the “numbers” from HbA_{1c} in % with serum glucose in mmol/L.
- A number of countries in the European Union as well as New Zealand in the Southern Hemisphere have already initiated the change to the new SI units.

6 Blood glucose monitoring

Blood glucose monitoring is an essential aspect of care for people with type 1 diabetes and integral to current standard intensive diabetes management is self-monitoring of blood glucose (SMBG). Such monitoring is performed intermittently, four to six times each day, usually before and/or after main meals using an accurate, portable blood glucose meter (DCCT Research Group 1993).

More frequent SMBG is typically required in certain circumstances. For example, timely targeting of SMBG within a day or at night can help to prevent hypoglycaemic events or detect them early in their course (Allen and Frier 2003). Such targeting also improves safety in planning and undertaking physical activity and cognitively demanding activity, for example at school (Bui and Daneman 2006), in the work place and when driving (Cox et al 2006). When hypoglycaemia does occur, serial SMBG helps to ensure that it is adequately treated (DCCT Research Group 1993). Infants and young children typically require more frequent blood glucose measurement because they usually cannot identify symptoms of hypoglycaemia and signs may not be apparent to their parents or carers (Ambler and Cameron 2010). In addition, during sick day management, when blood glucose may become elevated with developing ketoacidosis, frequent SMBG is necessary, as is ketone measurement (Laffel et al 2006). Ketoacidosis and sick day management are covered in Chapter 17.

For any individual with diabetes, personalised education by qualified and experienced health professionals in appropriate blood glucose targets and timing of SMBG, interpretation of documented SMBG serial profiles and trends across and between days, is essential. Such education helps the person, or their parents/carers, to accurately adjust insulin doses. This also enables matching of insulin requirements with carbohydrate intake and estimation of correction insulin boluses appropriately (DAFNE Study Group 2002; McIntyre 2006) (ISPAD 2009).

Despite being a cornerstone of care in type 1 diabetes, SMBG performed by intermittent capillary blood glucose testing only provides a cross-sectional 'snapshot' of blood glucose levels. This limitation may lead to undetected peaks and troughs in blood glucose occurring between times of SMBG testing, which can lead to erroneous decisions about insulin dosing and carbohydrate intake (Fiallo-Scharer and Diabetes Research in Children Network Study Group 2005). More frequent SMBG testing in intensive diabetes management is a predictor of lower glycated haemoglobin (HbA_{1c}) levels (Schutt et al 2006); however, sampling of blood glucose using a fingerprick device during SMBG is demanding for the person with diabetes, and often the frequency of testing actually performed is suboptimal (Hansen et al 2009).

Continuous glucose monitoring (CGM) systems measure glucose in the interstitial fluid, to provide semicontinuous information about glucose levels. CGM systems may allow detection of fluctuations that would not have been identified with self-monitoring alone. Currently, the regular use of CGM is not common practice in care of people with type 1 diabetes, either within Australia or in other countries with well-developed health-care systems (2007).

There are two types of CGM systems that measure interstitial glucose calibrated to SMBG:

- 'real-time CGM systems' that continuously provide the calibrated blood glucose concentration on a personalised display

- ‘retrospective CGM systems’ that measure the glucose concentration during a certain time span; the information is stored in a monitor and can be downloaded and the calibrated data only accessed later. The primary application of retrospective continuous monitoring systems is their potential utility as a review tool for health care providers in collaboration with the person with diabetes, to identify the presence and possible causes of fluctuations in blood glucose.

Each of these systems may be used with various insulin regimens, including continuous subcutaneous insulin infusion (CSII) systems or multiple daily subcutaneous injection (MDI) approaches to therapy.

This chapter examines the effectiveness of real time CGM (Question 6.1) and retrospective CGM (Question 6.2) on HbA_{1c}, fluctuations of blood glucose and severe hypoglycaemia (SH). Cost effectiveness was also examined (Section 6.3), but was not systematically reviewed and is provided as narrative text only. For the purposes of these questions, standard management includes capillary SMBG at least four times per day, and an HbA_{1c} level undertaken every 3–4 months. Blood glucose targets are covered in Chapter 5.

6.1 Continuous real time monitoring vs standard management

Question 6.1

Does continuous real-time glucose monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

HbA_{1c}, glycated haemoglobin; CGM, continuous glucose monitoring

The detailed systematic reviews of these questions are in Chapter 6 of the accompanying technical report, and the evidence matrixes are in Sections C6 of Appendix C

The systematic review of continuous real-time monitoring versus standard management identified 13 publications that met the inclusion criteria, of which 12 were randomised controlled trials (RCTs) (Chase et al 2003; Chase 2005; Deiss et al 2006; Hirsch et al 2008; JDRF CGM Study Group 2008; Cosson et al 2009; Hermanns et al 2009; JDRF CGM Study Group 2009; Logtenberg et al 2009; O'Connell et al 2009; Peyrot and Rubin 2009; Raccach et al 2009). The search also identified a Cochrane protocol on this topic (Langendam et al 2009). The authors were contacted and provided the final version of their systematic review.

Langendam et al (In preparation), the Cochrane Review that was not published at the time of the current systematic review, included all of the studies of real-time CGM systems captured by the search. Langendam et al (In preparation) were unable to pool the results and perform a meta-analysis. All RCTs compared CGM with SMBG; there were no head-to-head comparisons between CGM systems. Glycaemic control was an outcome measure in all RCTs, and most studies reported change in HbA_{1c} level. In power analyses, a clinically significant difference of 0.5% HbA_{1c} was often used to calculate sample size. SH and diabetic ketoacidosis (DKA) occurred infrequently; thus, most studies were underpowered to detect differences for these outcomes. Results of the cross-over trial by Logtenberg et al (2009) were excluded, because they included people from an outpatient clinic who used continuous intraperitoneal insulin infusion (CIPII). At present, CIPII is only available in a few European countries (mainly France, Sweden and The Netherlands); therefore, it is not relevant to Australia.

Children

In children, a RCT reported in Langendam et al (In preparation) investigated the effectiveness of real-time CGM systems (JDRF CGM Study Group 2008). In this trial, the CGM group used three different types of CGM systems, and 114 children (aged 8–14 years) were included. During the 6-month study period, HbA_{1c} levels declined in both the CGM and SMBG groups. The difference in change was not statistically significant (change in HbA_{1c} –0.37% vs –0.22%, mean difference [MD] –0.15%, 95% confidence interval [CI]: –0.42 to 0.12). However, the proportion of patients who improved their HbA_{1c} level by at least 0.5% was significantly higher in the CGM group (54% vs 31%, relative difference [RD] 23%, 95%CI: 5% to 40%). The occurrence of SH after 6 months of follow-up was lower in the CGM study arm, but the difference was not statistically significant (7% vs 12%, RD –5%, 95%CI: –16% to 6%). At baseline and after 6 months, glucose values were measured with (blinded) CGM in both study arms. The change in mean number of minutes per day with glucose level below 3.9 mmol/L was not different between the CGM and SMBG group (–2 vs 0 minutes, p=–0.29). The change in number of minutes per day with glucose level above 10.0 mmol/L (hyperglycaemia) was also not different, although the change was larger in the CGM group (–102 vs –36 minutes, p=0.58).

Adolescents

Two RCTs addressed the adolescent population (Hirsch et al 2008; JDRF CGM Study Group 2008). In one RCT (JDRF CGM Study Group 2008), which included 110 adolescents aged 15–24 years, the CGM group used three different CGM devices. In the other trial (Hirsch et al 2008), which included young people aged 12–18 years, all had been previously treated with an insulin pump for at least 6 months. The duration of both studies was 6 months. In each of the two trials, both the CGM group and the SMBG group had lower HbA_{1c} levels 6 months after baseline, but there was no statistically significant difference in change in HbA_{1c} between the two study arms, and no difference in absolute HbA_{1c} level (8.0% vs 8.2%, MD –0.19, 95%CI: –0.85 to 0.47). Furthermore, the proportion of patients who improved their HbA_{1c} level by at least 0.5% was equal in both groups. SH and DKA events were infrequent, and there were no significant differences between the groups. At baseline and after 6 months, glucose values were measured with CGM in both groups in the JDRF trial (2008). The number of minutes per day with glucose level <3.9 mmol/L (hypoglycaemia) and with glucose level >10.0 mmol/L (hyperglycaemia) decreased for both groups between the two time points, but with largely the same amount (JDRF CGM Study Group 2008).

Adults

In adults, the effectiveness of real-time CGM systems was investigated in six trials (Hirsch et al 2008; JDRF CGM Study Group 2008; Cosson et al 2009; Hermanns et al 2009; Logtenberg et al 2009; Peyrot and Rubin 2009). One of these trials included patients from 12 years of age, and reported the results for HbA_{1c} for adults separately (Hirsch et al 2008). The detailed outcomes of these trials are provided in the technical document. In summary, shorter term (<6 months duration) studies showed no statistically significant differences in glycaemic control for the real-time CGM systems, although one study found a relatively large and clinically relevant difference in change in HbA_{1c} (0.69%) between the CGM and SMBG groups (2009). Longer term (≥6 months) glycaemic control outcomes showed conflicting results: one RCT (with low risk of bias) showed a statistically and clinically significant greater improvement in HbA_{1c} for the CGM group (MD in change –0.52%, 95%CI: –0.72 to –0.32) (JDRF CGM Study Group 2008) while in another RCT (moderate risk of bias), there was no difference (Hirsch et al 2008).

In people with poorly controlled diabetes (HbA_{1c} >8.0%), three RCTs using real-time CGM were performed (Deiss et al 2006; Cosson et al 2009; Raccach et al 2009). There was limited evidence for improved glycaemic control. The change in HbA_{1c} was larger in the CGM group than in the SMBG group in all three RCTs, but statistically significant in only one high-quality RCT (MD in change -0.60%, 95%CI: -1.00 to -0.20) (Deiss et al 2006). In one of these RCTs (Raccach et al 2009), a subgroup of patients who were fully protocol-compliant (including CGM sensor wear ≥70% of the time) was analysed based on a prespecified analysis. Fully compliant CGM users showed a larger improvement in HbA_{1c} than CGM users in the total group (mean change in 6 months -0.96%, standard deviation [SD] 0.93 vs -0.81%, SD 1.09%). In this per-protocol analysis, the difference in improvement between the CGM and SMBG groups was statistically significant (p-value for difference between study arms = 0.004), in contrast to the intention-to-treat analysis (Raccach et al 2009).

In conclusion, there is some evidence favouring the effectiveness of real-time CGM use to improve HbA_{1c} levels, including in those with poorly controlled diabetes. Against intuitive expectations, real-time CGM systems are not associated with lower incidence of severe hypoglycaemia in type 1 diabetes, although most studies were underpowered to detect a difference in this endpoint, and studies that include patients with hypoglycaemia unawareness are lacking. In addition, some real-time continuous monitoring systems have a hypoglycaemia alarm and this potentially valuable tool to help prevent severe hypoglycaemia was not specifically addressed in the RCT evidence.

Evidence statements	
Q6.1	There is insufficient evidence to support routine use of real-time continuous glucose monitoring (CGM) to improve HbA _{1c} and reduce severe hypoglycaemia.
Recommendations	
R6.1	Real-time CGM may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).
Practice points	
PP6.1.1	Real-time CGM could be considered for use by specialist units, in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. In these situations, use of a hypoglycaemia alarm in a real-time monitoring system may help to treat hypoglycaemia in a timely manner and prevent severe episodes of hypoglycaemia.
PP6.1.2	When combined with CSII therapy, evidence from sensor-augmented CSII studies supports use of real-time CGM to improve HbA _{1c} when they are used at least 70% of the time.
PP6.1.3	It is essential that individuals using these real-time monitoring systems be provided with education in the correct use of the real-time monitoring device and the correct interpretation of results.
PP6.1.4	Real-time CGM systems are not currently reimbursed by the NDSS or health insurance funds. Given current cost constraints, they are most likely to be useful over short periods of time, to aid profile setting and trouble shooting in glycaemic control.
CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA _{1c} , glycated haemoglobin; NDSS, National Diabetes Services Scheme	

6.2 Continuous retrospective monitoring vs standard management

Question 6.2

Does continuous glucose monitoring (retrospective systems) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

HbA_{1c}, glycated haemoglobin; CGM, continuous glucose monitoring

The detailed systematic reviews of these questions are in Chapter 6 of the accompanying technical report, and the evidence matrixes are in Sections C6 of Appendix C

Nine publications met the inclusion criteria for this question. Of these, two were systematic reviews (Chetty et al 2008; Golicki et al 2008) and seven were RCTs (Chase et al 2001; Chico et al 2003; Ludvigsson and Hanas 2003; Tanenberg et al 2004; Lagarde et al 2006; Yates et al 2006; Deiss et al 2006b); with two in adults alone (Chico et al 2003; Tanenberg et al 2004); four in children alone (Chase et al 2001; Ludvigsson and Hanas 2003; Lagarde et al 2006; Deiss et al 2006b); and one in adults and children (Yates et al 2006). The search also identified a Cochrane protocol on this topic (Langendam et al 2009); the authors were contacted and provided the final version of this systematic review (In preparation). This unpublished Cochrane review included all of the studies of CGM systems captured by our search, and here, we report only on the evidence from RCTs in retrospective CGM systems. The seven studies included in Langendam's systematic review were also included in the previous systematic review conducted by Chetty et al (2008).

Chetty et al (2008) found that, compared with SMBG, retrospective CGM systems were associated with a nonsignificant reduction in HbA_{1c} (0.22%; 95%CI -0.439% to 0.004%; p=0.055). Sensitivity analysis using the three high-quality studies gave similar results (0.044%; 95%CI -0.35% to 0.26%; p=0.775). When the paediatric population was analysed separately, a significant reduction in HbA_{1c} in favour of retrospective CGM systems was observed (0.37%; 95%CI -0.71% to -0.02%; p=0.036). The authors concluded that there is insufficient evidence to support retrospective CGM systems as more beneficial than intensive SMBG in improving HbA_{1c} in patients with type 1 diabetes. There may be a benefit in the paediatric population. Langendam et al (2009), in adults, reported results that were consistent with Chetty et al (2008), showing no clear benefit of retrospective CGM systems. However, Langendam et al (2009) found the evidence for retrospective CGM systems in children to be conflicting: significantly lower in some studies (Ludvigsson and Hanas 2003; Lagarde et al 2006) and significantly higher in another (Chase et al 2001).

HbA_{1c} levels for the CGM group at the end of the study were reported. In one RCT, the difference in change after 3 months was not statistically significant (Deiss et al 2006). In another RCT, the absolute HbA_{1c} level was significantly lower in the CGM group, but the difference in change in HbA_{1c} did not reach significance (Lagarde et al 2006). In terms of patients poorly controlled at study entry, three RCTs (of retrospective CGM systems) were performed with commencing HbA_{1c} >8.0%, the evidence for improved glycaemic control was conflicting. There was no definite evidence for any effect of retrospective CGM systems on SH rates or variability in blood glucose levels.

In conclusion, use of retrospective CGM systems compared with current standard monitoring does not provide clear benefit on glycaemic control or hypoglycaemia. The exception to this finding may be in the paediatric population.

Evidence statements	
Q6.2	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA _{1c} and reduce severe hypoglycaemia.
Recommendations	
R6.2	Retrospective CGM systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for children and adolescents (Grade C).
Practice points	
PP6.2.1	Retrospective CGM systems could be considered for use by specialist units, in specific patient populations such as those with suspected nocturnal hypoglycaemia.
PP6.2.2	Retrospective CGM systems are not currently reimbursed by the NDSS or health insurance funds. These systems are designed to be used continuously over short periods of time (e.g. up to 6 days continuously), to aid profile setting and trouble shooting in glycaemic control.
CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HbA _{1c} , glycated haemoglobin; NDSS, National Diabetes Services Scheme	

6.3 Cost and cost-effectiveness of real-time and retrospective monitoring versus standard management

This section was not systematically reviewed and as such, there are no recommendations or practice points. The narrative provides background information only; no evidence-based guidelines are referenced in this section.

(Eastman et al 2003) examined the cost-effectiveness (preliminary analysis) of the GlucoWatch Biographer. This study was also identified by Langendam et al in their systematic review. Because the GlucoWatch Biographer is not available in Australia, we have not summarised the findings of this study. The JDRF et al (2008) study (included in the systematic review for question 6.1), has planned a cost-effectiveness study of real-time CGM, but this analysis has not yet been published. Thus, no conclusions could be drawn, especially in the context of current limited demonstrable effectiveness of CGM.

7 Insulin and pharmacological therapies

When regular human insulin is administered subcutaneously, it is present in multimeric forms, leading to delayed and variable absorption. Therefore, altered forms of human insulin – known as insulin analogues – have been developed to deliver therapeutic insulin in a way that better reflects bolus physiological insulin requirements, both prandial (i.e. at meal times) and basal (i.e. between meals, including overnight). Rapid-acting insulin analogues are delivered as a sub-cutaneous bolus injection just prior to meal commencement compared with regular human insulin, which should be administered approximately 30 minutes before the meal.

The systematic review investigated a range of insulin analogues for their effectiveness in reducing glycated haemoglobin (HbA_{1c}) levels and hypoglycaemia. The analogues reviewed were the rapid-acting analogues, insulin lispro, insulin aspart and insulin glulisine; and the basal analogues, insulin glargine and insulin detemir. The analogues were compared with rapid-acting human or regular insulin, and basal-acting neutral protamine Hagedorn (NPH) insulin zinc. It is beyond the scope of this Guideline to address the detailed process of formulating individualised insulin regimens and insulin administration; the consumer and health professional reading materials in Appendix D provides access to written material in practical aspects of insulin therapy.

7.1 Insulin analogues versus human insulin

Question 7.1

(i) How effective are insulin analogues versus human insulin at reducing hypoglycaemia and HbA_{1c}?

(ii) What is the relative effectiveness between insulin analogues on hypoglycaemia rates and HbA_{1c}?

(iii) What are the cost and cost-effectiveness of insulin analogues on hypoglycaemia rates and HbA_{1c}?

HbA_{1c}, glycated haemoglobin

The detailed systematic reviews of these questions are in Chapter 7 of the accompanying technical report, and the evidence matrixes are in Sections C7 of Appendix C

7.1.1 Comparison of insulin analogues and human insulin in reducing hypoglycaemia and HbA_{1c}

In comparing insulin analogues with human insulin, the literature search identified 15 Level I studies in type 1 diabetes, three of which were comprehensive and were included for analysis (Banerjee et al 2007; Tran et al 2007; Singh et al 2009). Three, more recent, Level II studies were included in the analysis for rapid-acting analogues (Chatterjee et al 2007; Bartley et al 2008; Chase et al 2008). The studies covered paediatric, adolescent and adult populations. In general, the randomised controlled trials (RCTs) were limited by the lack of blinding in treatment assignment, and the lack of reported blinding of outcome assessor, patient and care giver. Most of the included trials were multicentre and were sponsored by industry, and many were also multinational. In addition, due to data availability for the end-points examined, the meta-analyses reported commonly did not include the same studies in

the HbA_{1c} and the hypoglycaemia forest plot data, making valid comparisons across these outcomes for these therapies problematic.

Adults, rapid-acting and basal-acting analogues

In adults, compared with regular human insulin, use of insulin lispro resulted in an HbA_{1c} lower by 0.09% units and a 20% lower risk of severe hypoglycaemia (Singh et al 2009). The rate of total hypoglycaemia was similar between groups. Subgroup analysis by method of administration did not reveal substantial differences in treatment effects between patients using multiple daily injections (MDI) and those using continuous subcutaneous insulin infusion (CSII). Insulin aspart also resulted in a slightly lower mean HbA_{1c} concentration (0.13%) compared with regular human insulin (Singh et al 2009). However, there were no differences between groups in the risk of severe hypoglycaemia or the rate of overall hypoglycaemia.

In adults, compared with NPH insulin, use of insulin glargine resulted in a statistically significantly lower HbA_{1c} (by 0.11% units and, more recently, by 0.19%) (Chatterjee et al 2007). There was a high degree of heterogeneity regarding hypoglycaemia, which was largely negated when the study of shortest duration (4 weeks) was removed from the meta-analysis; this study demonstrated the largest risk reduction in favour of insulin glargine. Overall, no statistically significant differences were found in HbA_{1c} between insulin detemir and NPH insulin (Singh et al 2009); however, a more recent single study (Bartley et al 2008) reported a lower HbA_{1c} by 0.22% with insulin detemir. In these studies, the risk of severe hypoglycaemia was statistically and clinically significantly reduced – by 26% (Singh et al 2009) and 69% (Bartley et al 2008) – with use of insulin detemir compared with NPH insulin, while overall hypoglycaemia was similar in the two groups.

Children and adolescents, rapid-acting and basal-acting analogues

In children and adolescents, the data demonstrated few benefits of insulin analogues compared with human insulin for the outcomes examined. In children, pooled analysis of trials comparing insulin lispro with regular human insulin found no statistically significant differences in HbA_{1c} or hypoglycaemia (Singh et al 2009). In adolescents, one study found that nocturnal hypoglycaemia was significantly reduced by 39% (Singh et al 2009). Another study that compared insulin aspart and human insulin in children found no statistically significant differences. Similarly, in a trial comparing insulin aspart and human insulin in patients aged 6–18 years, there were no statistically significant differences for these outcomes. Furthermore, there were no differences in HbA_{1c} or hypoglycaemia between insulin glargine and conventional insulins (mostly NPH insulin) in children or adolescents (Chase et al 2008). Comparing insulin detemir and NPH insulin in adolescents, one trial showed no difference in HbA_{1c}, but a small and significant effect in favour of insulin detemir for nocturnal hypoglycaemia (reduced by 15%) and overall hypoglycaemia (Singh et al 2009).

Summary

Overall, insulin analogues appear to offer relatively few clinical advantages over conventional insulins in the management of most people with type 1 diabetes, although high-quality RCTs are lacking. The clearest advantage for insulin analogues is in adults, where some studies show a slight advantage in HbA_{1c} (0.1–0.2%) and others show reduced hypoglycaemia, particularly for nocturnal hypoglycaemia and severe hypoglycaemia in some studies. This advantage in hypoglycaemia is notable, because many clinical trials excluded people with a history of recurrent severe hypoglycaemia.

A recent report of combined phase III and IV studies Mullins et al (2007) found that, compared with NPH insulin, use of insulin glargine in type 1 diabetes reduced either HbA_{1c} or hypoglycaemia. Although systematic, this study appeared to be highly selective and biased in terms of the study series included for analysis. The study demonstrated an inverse relationship between HbA_{1c} and severe hypoglycaemia, and after adjusting for study endpoint HbA_{1c}, there was some evidence for a reduction in symptomatic and severe hypoglycaemia in patients treated with glargine compared with NPH.

7.1.2 Comparisons of insulin analogues

The systematic review identified one Level 1 study of fair quality (Singh et al 2009), which included two RCTs (Bode et al 2002; Pieber et al 2007); it also identified three further RCTs (Dreyer et al 2005; Weinzimer et al 2008; Heller et al 2009). Populations studied included children, adolescents and adults, and the studies were multicentre and multinational.

None of five studies showed a statistically significant difference in mean change from baseline HbA_{1c} when different insulin analogues were compared. One study showed a lower relative risk of all nocturnal, all severe and symptomatic nocturnal hypoglycaemia for insulin detemir compared with insulin glargine (Pieber et al 2007). However, another study found no difference in frequency of any types of hypoglycaemia between these insulins (Heller et al 2009).

For CSII therapy, one study found no statistically significant difference in HbA_{1c} between aspart, regular and lispro insulin in adults (Bode et al 2002). Another study of CSII therapy found no significant difference between insulin aspart and insulin lispro in HbA_{1c} or hypoglycaemia (Weinzimer et al 2008).

Some people with type 1 diabetes will prefer certain insulin types and regimens to others, even though a consistent metabolic advantage may be difficult to demonstrate. Furthermore, some insulins may have other relative advantages; for example, insulin detemir has been shown in some high-level longer term studies to cause less weight gain than regimens using other basal insulins (especially NPH insulin) (Bartley et al 2008).

7.1.3 Cost-effectiveness studies

Twelve studies addressed the cost effectiveness of insulin analogues compared with human insulins. These studies included one meta-analysis (Tran et al 2007), three studies of rapid-acting insulin analogues (Banerjee et al 2007; Reviriego et al 2008; Pratoomsot et al 2009), and seven studies of long-acting insulin analogues (Palmer et al 2004; Grima et al 2007; Palmer et al 2007; Brixner and McAdam-Marx 2008; Cameron and Bennett 2009; Gschwend et al 2009; Tunis et al 2009). As severe hypoglycaemia has a significant impact on the total cost of diabetes, the studies found that the use of insulin analogues might be associated with reductions in annual costs by reducing the frequency of severe hypoglycaemia. However, the overall financial effect may be cost neutral or cost saving when total costs are considered, because insulin analogues cost more. Studies of quality-adjusted life years and quality-adjusted life expectancy in developed countries generally demonstrate that insulin analogues are economically justified in the treatment of type 1 diabetes.

Evidence statements	
Q7.1.1	In adults, Level I studies of insulin analogues show a small (0.1–0.2%) but statistically significant reduction in HbA _{1c} with insulin analogues compared to human insulin; this effect is not seen in children. Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with NPH insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.
Q7.1.2	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA _{1c} . Overall, Level II evidence shows no significant difference between insulin analogues in relation to reduction of hypoglycemia.
Recommendation	
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).
Practice points	
PP7.1.1	Basal and rapid-acting insulin analogues may reduce the risk of hypoglycaemia compared to human insulin.
PP7.1.2	Insulin analogues may be useful in people who have a history of recurrent nocturnal or severe hypoglycaemia.
PP7.1.3	In some people, basal and rapid-acting insulin analogues may improve an individual's HbA _{1c} level without increasing hypoglycaemia.
PP7.1.4	Rapid-acting insulin analogues may be useful in people who match bolus insulin doses to carbohydrate intake.
PP7.1.5	Personal preference and quality of life should be considered when individualising insulin therapy, including analogue therapy versus human insulin.
HbA _{1c} , glycated haemoglobin	

7.2 Continuous subcutaneous insulin infusion versus multiple daily injections

Intensive diabetes management can be delivered using either MDI as part of a basal-bolus insulin approach, or rapid-acting insulin in insulin pump therapy as CSII. Since the Diabetes Control and Complications Trial publication in the early 1990s, MDI has included three or more injections of subcutaneous insulin each day for adults; CSII therapy has also progressively improved. Thus, for the purposes of this question, MDI is defined as three or more injections per day; modern CSII pump therapy is defined as those pumps that are available in Australia or overseas and have not become obsolete.

Question 7.2

(i) How effective are modern CSII pumps versus MDI at reducing hypoglycaemia and HbA_{1c} and improving quality of life (QoL) (DQOL or SF-36 or others)?

(ii) How effective are sensor-augmented CSII pumps versus MDI at reducing hypoglycaemia and HbA_{1c}, and improving QoL?

(iii) What are the costs (upfront plus ongoing) and cost effectiveness of treatment with CSII pumps versus MDI?

CSII, continuous subcutaneous insulin infusion; DQOL, diabetes quality of life; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; QoL, quality of life; SF-36, short-form health survey

MDI is defined as three injections per day for adults, and at least three injections per day for children; modern pumps are defined as those that are available in Australia or overseas, and are not obsolete.

The detailed systematic reviews of these questions are in Chapters 7 of the accompanying technical report, and the evidence matrixes are in Sections C7 of Appendix C.

7.2.1 CSII versus MDI

The systematic literature review addressing question 7.2 (i) identified three systematic reviews (Fatourechhi et al 2009; Pankowska et al 2009; Misso et al 2010) and two additional RCTs (Opipari-Arrigan et al 2007; Bolli et al 2009). Ten of the studies included in the meta-analysis of HbA_{1c} by Misso et al (2010) were published before 2000; they were therefore excluded from our modern CSII and MDI criteria. Some studies recently published (e.g. Bolli et al 2009), included first generation CSII devices, which do not have some features of the most modern pumps such as a bolus calculator. We reanalysed the data from the studies that met our inclusion criteria, with the addition of the study by Bolli et al (2009). A random-effects model was used, and results are reported as weighted mean difference at endpoint.

Glycaemic control

The studies included in this analysis involved 697 children and adults with type 1 diabetes (CSII n=351, MDI n=346); 204 were aged less than 18 years and 493 were 18 years or older. Overall, the mean difference in HbA_{1c} at treatment end was -0.2% in favour of CSII (95% confidence interval [CI]: -0.28 to -0.12, p<0.00001), with low heterogeneity across the studies. In adults, the mean difference in HbA_{1c} was -0.16% (95%CI: -0.33 to 0.01, p=0.06) in favour of CSII. In children, the mean difference in HbA_{1c} was -0.25% (95%CI: -0.46 to -0.05, p=0.01) in favour of CSII. This is in keeping with the meta-analysis by Pankowska and colleagues, which showed a significantly lower HbA_{1c} value in children treated with CSII compared with MDI by -0.24% (95%CI: -0.41 to -0.07, p<0.001) (Pankowska et al 2009).

Hypoglycaemia

Misso et al (2010) suggested that data from the 17 studies in their meta-analysis reporting on hypoglycemia indicated that there was no relevant benefit of one intervention over the other for reducing nonsevere hypoglycaemic events. However, they suggested that CSII might be better than MDI for reducing the incidence of severe hypoglycaemic events. Pankowska et al (2009) only assessed episodes of severe hypoglycaemia: four included studies reported episodes of severe hypoglycemia and meta-analysis showed no statistically significant difference between CSII and MDI (pooled relative risk [RR] 0.87, 95%CI: 0.06 to 11.66, $p=0.87$). The meta-analysis of hypoglycaemia by Fatourechi et al (2009) demonstrated some evidence for a reduction in severe hypoglycaemia, which was not statistically significant (pooled odds ratio [OR] 0.48, 95%CI: 0.23 to 1.00), and nonsignificant reduction in nocturnal hypoglycaemia (pooled OR 0.82, 95%CI: 0.33 to 2.03). There was no statistically significant difference in minor hypoglycemia episodes per patient week in adolescents and adults enrolled in cross-over trials comparing CSII with MDI (pooled RR -0.08 ; 95%CI: -0.21 to 0.06), whereas children enrolled in parallel trials had significantly more episodes with CSII (pooled RR 0.68; 95%CI: 0.16 to 1.20, $p=0.03$). The authors noted that the main limitation of their study was the paucity of data in patients with a history of severe hypoglycaemia and patients with hypoglycaemia unawareness (Fatourechi et al 2009). However, Bolli et al (2009) found the incidence of total hypoglycaemia, nonsevere hypoglycaemia, symptomatic hypoglycaemia and asymptomatic hypoglycaemia was similar in both groups; only two participants in both groups experienced one severe hypoglycaemic event. It is noteworthy that the event rates for hypoglycaemia were low in all these studies, which affects the power to detect between group differences. Furthermore, the studies were not powered for the outcome of severe hypoglycaemia.

Quality of life

Of the studies included in the Cochrane review by Misso et al (2010), eight measured QoL using validated measurement tools. Four studies used the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ); two of these studies enrolled people younger than 18 years. In all four studies, the CSII group scored higher (representing better treatment satisfaction) than the MDI group. This difference was statistically significant in two of the four studies. Of the two studies that used the validated diabetes QoL youth scale, one study in adults reported a higher score, representing better QoL in the CSII group than the MDI group. The other study, which enrolled people younger than 18 years, did not report scores but noted that there was no difference between groups. Two studies that used the validated diabetes QoL scale (DQoL) found that the MDI group scored lower (representing better QoL than the CSII group), but this was not statistically significant. The SF-12 questionnaire, SF-36 general health perceptions scale, and the paediatric QoL inventory (PedsQL) revealed that CSII was favoured over MDI for perception of better mental health, perception of better general health, and better QoL, respectively.

Pankowska et al (2009) reported that QoL was measured in four of the included studies, but meta-analysis was not performed due to differences in participant characteristics and tools used. DTSQ scores were significantly higher in patients treated with CSII compared with MDI at study end (30.6 ± 3.7 vs 21.9 ± 3.8 , $p<0.001$) (Weintrob et al 2004). DQoL improved from baseline to study end in young children treated with CSII vs MDI ($\Delta -0.24\pm 0.25$ vs -0.08 ± 0.19 , $p=0.03$) (Wilson et al 2005). Fox et al (2005) measured DQoL separately in mothers and fathers, with mothers of patients on MDI reporting a greater negative impact of diabetes on family life, and fathers in the MDI group reporting significantly higher scores on the stress index (Fox et al 2005). There was no difference in DQoL scores between groups in the fourth study (Doyle et al 2004).

Bolli et al (2009) found a significant increase in DTSQ treatment satisfaction score in the CSII group compared with the MDI group (3.1, 95%CI: 0.1 to 6.1, $p=0.042$). Opipari-Arrigan et al (2007) measured diabetes-related QoL with a validated tool – the PedsQL. They found a significant improvement in diabetes symptoms in both groups compared with baseline, and a significant decrease in diabetes related worry in the CSII group.

In summary, there is evidence from the studies reviewed suggesting that, on average, there is some advantage for CSII over MDI in terms of HbA_{1c} levels, especially in the paediatric population, and QoL for many people receiving CSII compared with MDI. Hypoglycaemia outcomes appear to be similar for CSII and MDI, although people at the highest risk of severe hypoglycaemia, who had a history of severe hypoglycaemia or a lack of hypoglycaemia awareness, were often excluded from these studies.

For intensive insulin diabetes regimens to be effective, whether using CSII or MDI, individuals need to be motivated, prepared to routinely undertake carbohydrate counting, and frequently self-measures of blood glucose (SMBG) and make correction dosage adjustments to insulin therapy. In addition, support by a skilled and well-resourced multi-disciplinary diabetes health care team is essential to intensive diabetes management, whether the insulin therapy be delivered by CSII or MDI. The studies varied as to whether the CSII group received more intensive education in SMBG, bolus correction and carbohydrate counting than the MDI group. Thus, the intensive diabetes-management approach, rather than CSII alone, may account for some of the observed advantages of CSII over MDI. To achieve sustained outcomes in intensive diabetes management, reliable follow-up in health care by the person with type 1 diabetes with their multidisciplinary diabetes health care team is highly desirable. This helps to ensure that self-management – including target setting – remains appropriate, and that patients continue to be motivated to optimise their health outcomes through self-care.

7.2.2 Sensor augments CSII versus MDI

The systematic review identified one study that met the inclusion criteria (Bergenstal et al 2010). In this multicentre ($n=30$) study of fair study quality, 485 people (329 adults, 156 children) were randomised to receive either sensor-augmented CSII or MDI (which did not include a real-time sensor component). Inclusion criteria were HbA_{1c} 7.4–9.5%, at least 3 months of MDI before enrolment, and monitoring of blood glucose levels at least four times per day. Exclusions included CSII in past three years, age under seven years, two or more severe hypoglycaemic episodes per year before enrolment, or current pregnancy. Baseline characteristics in both groups were similar. The primary outcome was change from baseline in HbA_{1c}, with the rate of severe hypoglycaemia as the secondary outcome. Follow-up measures occurred progressively at 3-month intervals for 12 months. Finally, for reasons of technical device training, participants in the CSII group received more contact with clinical staff members than did those in the MDI group during the first five weeks of the study.

The mean HbA_{1c} level at one year decreased from baseline (8.3% in all groups) to 7.5% in the sensor-augmented CSII group and 8.1% in the MDI group ($p<0.001$ for difference between groups). Significant differences were seen by 3 months of the trial and were maintained across the 12 months. The proportion of patients who reached the target HbA_{1c} of less than 7.0% was also greater in the CSII group (27%) than in the injection-therapy group (10%) ($p<0.001$) and was significantly greater in adults alone. Post-hoc analysis showed that in the sensor-augmented CSII group, the increased use of the sensor was associated with a greater reduction in HbA_{1c} at 12 months in the entire group ($p=0.003$). There was no significant difference between groups in the rate of severe hypoglycaemia, which was at a low rate in both groups. QoL was not assessed.

7.2.3 Cost-effectiveness studies

Campbell et al (2008) reported cost effectiveness as the incremental cost per severe hypoglycaemic episode avoided over six years. The analysis projected costs saved per severe hypoglycaemic episode, but the authors noted that current evidence for reduction in severe hypoglycaemia in people treated with CSII vs MDI was equivocal. The total additional costs of using CSII relative to improvements in glycaemic control, and the reduction in consequent diabetic complications, were considered and modelled by Cohen et al (2007), Roze et al (2005) and St Charles (2009), based on a lifetime horizon. All three studies used a base case of a 1.2% reduction in HbA_{1c} in those treated with CSII compared to MDI. Cohen et al (2007) projected the mean discounted lifetime direct medical costs associated with CSII was to be \$A123 402 ± 2113 in Australian adults compared with \$A88 760 ± 2055 for MDI (and in adolescents, \$A148 918 ± 2498 vs \$A107 139 ± 2320). The authors reported the incremental difference in costs of A\$34 642 translated into a cost per life-year gained (LYG) of \$A88 220 with CSII versus MDI in adults, and in the incremental difference of A\$41 779 translated into a cost per LYG of \$A77 851. These results are both near the threshold value of \$A76 000/LYG considered to represent good value for money in Australia.

All three studies (Cohen et al (2007), Roze et al (2005) and St Charles (2009)) also presented sensitivity analyses based on a reduction of HbA_{1c} of 0.51%, which is much closer to the reduction of HbA_{1c} of 0.2% reported in the systematic review of the clinical effectiveness of CSII versus MDI in this guideline. Costs were substantially higher for the smaller reduction in HbA_{1c}. However, the economic models did not find a reduction in the long-term complications of diabetes that may occur due to improved glycaemic control; nor did they include the associated costs, quality of life or survival implications.

Evidence statements	
Q7.2	<p>Across all individuals with type 1 diabetes, Level I evidence demonstrates a small but statistically significant reduction in HbA_{1c} with CSII compared to MDI. Level II evidence shows that CSII has a minor benefit for HbA_{1c} levels compared to MDI.</p> <p>There is no evidence to support a reduction in hypoglycaemia in adults. There is Level I evidence of a slight, but statistically significant increase in mild hypoglycaemia in children using CSII. There is no statistically significant evidence to support a reduction in severe and nocturnal hypoglycaemia in adults and children.</p> <p>Level II evidence shows an improvement in QoL with CSII compared to MDI. Level II evidence consistently shows improved treatment satisfaction with CSII compared to MDI.</p>
Recommendation	
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA _{1c} , reducing hypoglycaemia or improving QoL (Grade C).

Practice points	
PP7.2	<p>Individuals who may be likely to benefit from CSII pump therapy, as part of intensive diabetes management, are:</p> <ul style="list-style-type: none"> • some children and adolescents, including infants and young children, and pregnant women (ideally preconception) • individuals with microvascular complications of diabetes • individuals with reduced hypoglycaemia awareness • individuals (or their supervising adults) with desirable motivational factors; for example, those seeking to improve blood glucose control and having realistic expectations • individuals exhibiting desirable CSII treatment-related behavioural factors, including those who: <ul style="list-style-type: none"> - are able to perform carbohydrate counting - are currently undertaking four or more blood glucose tests per day - have reliable adult supervision (in paediatrics), and a history of good self-management skills (in adults) - are able to master the technical skills of CSII - are reliable in follow-up health care.
CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QoL, quality of life	

7.3 Metformin as an adjunct to insulin

Question 7.3

How effective is metformin plus insulin versus insulin alone at achieving glycaemic control (HbA_{1c} targets), reducing body weight, and reducing insulin requirement?

HbA_{1c}, glycated haemoglobin

The detailed systematic reviews of this question is in Chapter 7 of the accompanying technical report, and the evidence matrix is in Sections C7 of Appendix C

Metformin is a biguanide that is commonly used in the treatment of type 2 diabetes, where it improves glycaemic control without causing weight gain. Metformin lowers glucose by reducing hepatic glucose production (by inhibiting gluconeogenesis), and increasing insulin-stimulated glucose uptake in skeletal muscle and adipocytes. The effect of metformin on glucose metabolism is independent of residual β -cell activity; thus, the drug may have potential for use in patients with type 1 diabetes (Jacobsen et al 2009).

A recent meta-analysis (Vella et al 2010), which aimed to capture all published data from RCTs that used metformin in people of any age with type 1 diabetes, found five studies with relevant outcomes. The standardised mean difference (SMD) in %HbA_{1c} between treatment groups was -0.10, favouring metformin added to insulin (95%CI: -0.36 to 0.15, p=0.42). As there was some suggestion of heterogeneity (p=0.175), the authors performed a sensitivity analysis. Excluding the largest study (Lund et al 2008), the SMD in %HbA_{1c} between treatment groups was -0.30 (95%CI: -0.64 to 0.037, p=0.081). This translates into an absolute difference in HbA_{1c} of 0.28% lower in the metformin than in the placebo groups, with no evidence of heterogeneity (p=0.35).

The meta-analysis also analysed insulin dose in the five relevant studies (Vella et al 2010). The longest of these studies (up to 12 months duration) found a statistically significant reduction in daily insulin dose with metformin. The overall measure of effect was an SMD between treatment groups of -0.65 (i.e. 0.65 standardised units lower in the metformin than in the placebo groups; 95%CI: -0.92 to -0.39 units, p<0.001). This translates into an absolute difference in insulin-dose requirement of 6.6 U/day less in the metformin than in the placebo groups. The χ^2 test of heterogeneity was not statistically significant (p=0.41).

Seven studies were of sufficient duration to report data on changes in weight or BMI. Metformin reduced weight by 1.7–6.0 kg in two studies (Lund et al 2008; Jacobsen et al 2009), but had no effect on weight in three (Meyer et al 2002; Särnblad et al 2003; Khan et al 2006). A sustained and statistically significant reduction (mean 1.74 kg) was reported in the largest study, which was also of the longest duration (Lund et al 2008). There were insufficient data on weight for a formal meta-analysis of this outcome (Vella et al 2010).

There have been no rigorous, prospective studies of metformin in type 1 diabetes, in relation to diabetes complications outcomes. In type 2 diabetes, metformin is the agent of first choice. In a long-term Level II clinical trial of metformin in type 2 diabetes (UKPDS Group 1998a), metformin reduced microvascular and cardiovascular events in overweight people, and reduced diabetes-related death and all-cause mortality in this population. Metformin is known to have clinical value in women who have polycystic ovarian syndrome, where it may induce ovulation and aid fertility (Tang et al 2010).

Evidence statements	
Q7.3	Level I evidence demonstrates a small but not statistically significant reduction in HbA _{1c} with metformin plus insulin compared to insulin alone. Level II evidence shows no consistent effect of metformin plus insulin versus insulin alone on reduction in BMI or body weight. Level I evidence demonstrates a small but statistically significant reduction in insulin requirement with metformin plus insulin compared to insulin alone.
Recommendation	
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).
Practice points	
PP7.3.1	Metformin may be considered in individuals who have a high insulin requirement (e.g. overweight or obese subjects with total daily insulin dose at or above 2.0 IU/kg body weight), although the evidence demonstrates only a modest overall reduction in insulin requirement.
PP7.3.2	Since metformin may contribute to lactic acidosis development in metabolically unstable patients, it is relatively contraindicated in people who are at high risk of developing diabetic ketoacidosis or have high alcohol consumption.
PP7.3.3	Metformin is not contra-indicated in individuals with type 1 diabetes and co-existing polycystic ovary syndrome, and may be used to help induce ovulation.
PP7.3.4	Use of metformin in type 1 diabetes is not approved by the Therapeutic Goods Administration and is an 'off-label' indication in Australia. Prescribers should be aware that long-term adverse effects of metformin include an increased risk of vitamin B-12 deficiency, which should be monitored.

8 Health-care delivery

Multidisciplinary care is established practice for the management of individuals of all ages with type 1 diabetes. The specialist multidisciplinary diabetes care team includes:

- the person with diabetes and their family or carer
- a paediatric or adult endocrinologist or physician trained in the care of children, adolescents or adults with diabetes
- a diabetes educator
- an Accredited Practising Dietitian
- a psychologist or social worker

Each health care professional in the multi-disciplinary team needs to have knowledge of type 1 diabetes and chronic illness. The specialist health-care professional team leads and takes responsibility for diabetes care, including initiation of and changes to diabetes management, regular reviews, screening for complications and management of diabetes 'sick days'. To optimise health care delivery in type 1 diabetes, access to high quality health care is required (National Health Priority Action Council 2006). Diabetes Centres are one commonly accessible site in Australia multi-disciplinary health care services for the person with type 1 diabetes can be delivered (National Health Priority Action Council 2006). The person's general practitioner (GP) should be involved in care, including management of inter-current medical conditions and preventive health issues, such as immunisation schedules. The GP may also have an important role in psychosocial support, and in ensuring additional access to allied health services via Medicare for the person with type 1 diabetes. To ensure consistency and continuity of care, when the specialist team has seen a person with type 1 diabetes, the GP needs to be informed by the team of any changes to diabetes management, and the rationale for the changes, in a timely manner. This is particularly important if the changes are significant.

During pregnancy, the diabetes care team should also include an obstetrician. Depending on the health-care needs of the person with diabetes, other members of a team may include:

- a podiatrist
- an exercise physiologist
- an optometrist
- medical specialists, including an ophthalmologist, psychiatrist, nephrologist, cardiologist, gastroenterologist, dermatologist, adolescent physician and geriatrician, as appropriate.

The family's importance as members of a child's diabetes care team should be emphasised from the day of diagnosis (Pihoker et al 2009). Care provided by a multidisciplinary team results in fewer days in hospital, a higher level of participation in diabetes self-care practices, decreased re-admission rates, lower glycated haemoglobin (HbA_{1c}) levels and delayed development of complications (Levetan et al 1995; Zgibor et al 2000; Zgibor et al 2002).

The health-care needs of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse people should be specifically considered and professional support from

indigenous health-care workers included as part of multidisciplinary care. For Aboriginal and Torres Strait Islander peoples, strategies to improve access to comprehensive primary health care services and coordinated clinical care are important for management of chronic diseases such as diabetes (Bailie et al 2007). Such strategies include continuing medical education and training to improving health-care providers' knowledge and skills (Shephard and Gill 2003) (Clifford et al 2009).

The multidisciplinary team may not be available in rural and remote areas, particularly those with low population density. In such circumstances, a locally based paediatrician or physician, or a GP may provide primary care. These practitioners should have ready access to facilities and advice provided by the diabetes care team in regional centres. Telemedicine is an option for delivery of health care to remote and geographically isolated sites; this is covered in Section 8.2.

Across the lifespan, the majority of diabetes care occurs without the person requiring a hospital admission for a bed; that is, in an outpatient or ambulatory care out of hospital setting. Regular and continuing ambulatory diabetes care assessment is essential for maintaining optimal glucose control and monitoring for risk factors for acute and chronic complications.

After hours, people with type 1 diabetes should have access to the multidisciplinary diabetes specialist care team. For example, the team should be available to provide support in sick day care or when severe hypoglycaemia occurs, and to advise on the need for acute care hospital assessment.

8.1 Ambulatory care

Question 8.1

What is the effectiveness of ambulatory care versus hospital inpatient care of people with newly diagnosed disease?

The detailed systematic review of this question is in Chapter 8 of the accompanying technical report, and the evidence matrix is in Section C8 of Appendix C

8.1.1 At diabetes onset

Approaches to the initial management of patients newly diagnosed with diabetes who are not acutely unwell include:

- home management; this may involve one or two visits daily by a diabetes nurse for 2–3 days, followed closely by subsequent outpatient health care or in a private health care setting (Dougherty et al 1999)
- ambulatory care; this involves initial insulin therapy and education being delivered in an outpatient or private health care setting, and commonly involves up to 1 week of diabetes self-care education and review every day or every second day, initially (Clar et al 2007)
- hospital inpatient admission

Ambulatory, non-inpatient requiring care is standard for adults with newly diagnosed type 1 diabetes who are not unwell. In adults, no RCTs comparing routine hospital admission versus ambulatory care were found. In contrast, in children and adolescents, both inpatient and ambulatory care are practised.

A systematic review of routine hospital admission versus outpatient or home care in children at diagnosis of type 1 diabetes (Clar et al 2007) included two randomised controlled trials (RCTs) and five cohort studies, involving 626 children and adolescents. Of these, 298 received ambulatory care at diagnosis, either on an outpatient basis or at home, or in a combination of these types of care. Of the studies included in the review, only one was regarded as of good quality and of low risk of bias (Dougherty et al 1999). This was an RCT of 62 Canadian children who received traditional hospitalisation and outpatient follow-up or home management. The study found a significant between-group difference in glycaemic control at 2 and 3 years follow-up, with the ambulatory care group having a 0.7% lower HbA_{1c} (Dougherty et al 1999). None of the other studies found differences in glycaemic control between groups. Three studies measured patient knowledge, and found no significant difference between groups (Dougherty et al 1999; Siminerio et al 1999; Srinivasan et al 2004). The two studies that reported adverse events (diabetic ketoacidosis [DKA] and severe hypoglycaemia) found no difference between groups in either of these outcomes (Chase et al 1992; Dougherty et al 1999). Other psychosocial outcomes examined did not differ between groups; they included treatment adherence, family impact, coping and stress, treatment satisfaction, quality of life, child behaviour and sociability (Clar et al 2007).

There is Level IV evidence supporting a benefit of ambulatory care in terms of hospital re-admission rates (Swift et al 1993). In a 10-year retrospective cohort study from the United Kingdom of children with type 1 diabetes aged less than 15 years, 138 of 236 children were managed in the home or outpatient setting. Significantly fewer children who received home management were re-admitted for diabetes-related reasons ($p=0.004$). There was no difference in glycaemic control between the groups.

8.1.2 Type of educational needs at diabetes diagnosis in adults

As described above, while no RCTs addressing diabetes care settings in adults at diagnosis with type 1 diabetes were found, it is generally accepted that whatever the forum, diabetes education programs across the lifespan need to address series of key themes including: diabetes pathogenesis and natural history, nutrition, exercise, medications, goal setting and monitoring, acute and chronic complications of diabetes detection and management, psychological support and where appropriate, pregnancy related care (Australian Diabetes Society 2008; Hanas et al 2009; American Diabetes Association 2010). Thus, the educational needs for people with type 1 diabetes at diagnosis are many and those prioritised by people with diabetes may not be congruent with health professional expectations. One small qualitative peer-reviewed Australian study in adults ($n=70$) with average 6.3 years duration of type 1 diabetes reported in abstract form (Gilbert and Millard 2006) that the commonest themes retrospectively identified by those consumers requiring education at diabetes diagnosis were: food, on-line support services, personal stories and peer support and advice in insulin adjustment and physical activity. In contrast, the diabetes specialist health professionals surveyed ($n=49$) reportedly placed the following themes more prominently on their list: professional counselling and mental health care, legal and employment issues including driving and diabetes and information about alcohol and drugs, as well as pre-pregnancy care. This data reinforces that communication of education needs and wants is a two way process for people with diabetes and their health professional care team.

8.1.3 After diabetes onset

After the initial period of diagnosis and education (when frequent contact with the diabetes care team is usually required), individuals with diabetes should then continue to be reviewed regularly, at least 3–4 times per year. Those assessments typically include progress in glycaemia, including HbA_{1c} level and hypoglycaemia frequency and minimisation, and

self-management issues including in nutrition, physical activity and insulin therapy. In children, regular assessment of growth and puberty is also required. The reviews should include one major annual review with the multidisciplinary team, which in children should also include assessment of growth, blood pressure, and diabetes complications. In adults, the focus is similar at the annual review, and includes assessment of blood pressure, lipids, body weight, and diabetes complications status; in addition to blood glucose, parameters such as blood pressure, lipids and diabetes complications will require monitoring and management at the 3-4 monthly regular visits. All patients should have a GP who is regularly kept informed of the diabetes management.

As a chronic and complex disease, type 1 diabetes places a substantial and often relentless burden of treatment demands on the person with diabetes and their family (National Health Priority Action Council 2006). This burden can lead to reduced objective measures of adherence to pre-planned therapy, and may limit the capacity of the person with diabetes to fully participate in diabetes self-care (May et al 2009). An increasingly appreciated concept in chronic disease is to deliver health care that is minimally disruptive to the patient's lifestyle; this strategic approach aims to optimise quality of life, patient engagement in therapy and metabolic outcomes. Termed 'minimally disruptive medicine', the approach is facilitated by interdisciplinary coordination in clinical practice, and by personalising the health care delivered. For example, the health professional and patient share decision making, and set care priorities from the perspective of the person with diabetes (May et al 2009) These aspects of health-care delivery can be practised in an organised diabetes ambulatory care setting.

Evidence statements	
Q8.1	<p>Ambulatory care, delivered by a multidisciplinary team in a tertiary referral diabetes service, at diagnosis of type 1 diabetes in children over 2 years of age:</p> <ul style="list-style-type: none"> • results in a lower HbA1c (0.7%) at 3 years follow-up compared to in-hospital care at diagnosis • does not increase the risk of severe hypoglycaemia or diabetic ketoacidosis, or result in poorer levels of diabetes knowledge at 2 years follow-up compared to in-hospital care at diagnosis.
Recommendation	
R8.1	Children and adolescents presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).
Practice points	
PP8.1.1	<p>Groups for whom inpatient management is necessary at diagnosis include:</p> <ul style="list-style-type: none"> • individuals with diabetic ketoacidosis, significant comorbidities, inadequate social support or mental health issues • children under 2 years of age • those in geographically remote areas • non-English speakers.
PP8.1.2	In adults, ambulatory care at diagnosis is considered to be routine unless there are specific issues.
HbA _{1c} , glycated haemoglobin	

8.2 Telemedicine

Question 8.2

What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?

The detailed systematic review of this question is in Chapter 8 of the accompanying technical report, and the evidence matrix is in Section C8 of Appendix C

Australia is geographically large, but most of the population is concentrated in the southeast of the country. In many parts of Australia, the population density is low and health-care services are provided in regional sites some hundreds of kilometres away. This is often the case in type 1 diabetes, where multidisciplinary health-care services across a specialist team are typically desired and are necessary to optimise health care. Telemedicine, defined as the use of electronic information and communication technologies to provide and support health care when distance separates the participants (Field 1996), is one potential method by which health-care could be delivered in a personalised, patient-specific manner to remote and geographically isolated sites.

The systematic review identified a total of four relevant publications: two RCTs (Level II) (Ahring et al 1992; Biermann et al 2002), a comparative study (Level III-2) (Corriveau et al 2008), and a case-series study (Level IV) (Liesenfeld et al 2000). Technology methods used in the intervention included telephone modems, telemanagement and internet-based systems, and in some cases subsequently included health professional consultation and advice.

All four studies reported changes in HbA_{1c} as an outcome measure. They were based in North America and in European countries, with study duration 1–8 months. Of the four studies, only one (Ahring et al 1992), reported a statistically significant reduction in HbA_{1c} level compared with a control group, and another (Corriveau et al 2008) showed improvement in HbA_{1c} compared with baseline in patients using an internet-based insulin pump monitoring system. One other study (Biermann et al 2002) reported cost and time savings of a telemedicine intervention. The authors developed a cost-analysis scenario that showed a saving of €650 (~AUD \$900) per year per patient in achieving HbA_{1c} outcomes.

Telemedicine has the potential to aid in medical care in type 1 diabetes for rural and remote individuals; however, there have been few studies of this, especially in an Australian context. The four included studies reported were from international sources and were of limited methodological quality, involving small numbers of participants (42–94 per study).

Evidence statement	
Q8.2	There is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings.
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice point	
PP8.2	Technological mechanisms to support management can be a component of care for rural and remote patients, but should not replace face-to-face clinical care.

9 Education and psychological support

It is widely recognised that psychological and behavioural problems affect the outcomes and management of type 1 diabetes. The systematic review that examined the prevalence of psychological disorders (see Chapter 2 of the technical report) provided evidence for an increased prevalence of depression and anxiety in young people with type 1 diabetes. However, the evidence base to guide the use of screening tools for psychological disorders in type 1 diabetes is limited. Therefore, a systematic review was undertaken to examine the diagnostic performance of screening tools for psychological disorders in type 1 diabetes, to inform clinical practice. The results of this review are summarised in Section 9.2.

It is also widely recognised that intensive educational input and continuing support, frequently and at high levels, are key components of effective diabetes self-management. The Diabetes Control and Complications Trial (DCCT) provided unequivocal evidence that intensification of management reduces microvascular complications. More than 20 years after the DCCT was conducted, it is now clear that education is a fundamental component of diabetes care for people with type 1 diabetes. Educational and psychological interventions are frequently combined to improve knowledge, skills and self-efficacy across various aspects of diabetes self-management (Swift 2009). Therefore, it is difficult to ascertain the effectiveness of the educational component on metabolic and psychological outcomes. To address this issue, a systematic review examined the effects of educational and psychological interventions on metabolic and psychological outcomes. The results of this review are summarised in Section 9.3.

9.1 Psychological screening tools

Question 9.1

What is the diagnostic performance of the following screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?

ADS, Appraisal of Diabetes Scale, ATT19, Diabetes Integration Scale; BAI, Beck Anxiety Inventory; BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CDI, Children's Depression Inventory; CHQ, Child Health Questionnaire; EDE, Eating Disorders Examination; EDI, Eating Disorder Inventory; HADS, Hospital Anxiety and Depression Scale

The detailed systematic review of this question is in Chapter 9 of the accompanying technical report, and the evidence matrix is in Section C9 of Appendix C

A wide range of tools are available to screen for psychological disorders (including depression, anxiety and eating disorders) and behavioural problems in patients with type 1 diabetes and other chronic conditions. The tools examined in this systematic review were the Behaviour Assessment System for Children (BASC), the Children's Depression Inventory (CDI), the Child Health Questionnaire (CHQ) and the Eating Disorders Examination (EDE). The tools studied in adults were the Appraisal of Diabetes Scale (ADS), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI), the Diabetes Integration Scale (ATT19), the Eating Disorder Inventory (EDI) and the Hospital Anxiety and Depression Scale (HADS).

The systematic review examined the diagnostic performance of these screening tools in patients with type 1 diabetes. Outcomes examined were the diagnosis of anxiety, depression or eating disorder. The systematic review identified three studies: Cameron et al (2003), Hermanns et al (2006) and Lustman et al (1997).

The CHQ, evaluated by Cameron et al (2003), is a generic health status questionnaire that measures functional health and wellbeing in children aged 5–18 years, in the context of their family and social environments. In particular, the CHQ assesses the burden imposed by health problems on functional health and wellbeing of children (Landgraf et al 1996). In a study of 103 children in Victoria with type 1 diabetes and aged 7–12 years, Cameron et al (2003) assessed the validity of the CHQ as a screening tool for detecting ‘at-risk’ emotional and behavioural maladjustment in children with diabetes, compared with the BASC. The investigators found significant correlations between the CHQ Global Behaviour and Mental Health scales, and the BASC Externalizing and Internalizing scales, respectively. They concluded that sequential use of the CHQ, as a screening tool, followed by an established mental health measure such as BASC, may help to identify children with diabetes who are at risk for chronic maladjustment and poor health outcomes.

The study by Hermanns et al (2006) assessed the screening performance of different measures of depression, including the BDI, and the Problem Areas in Diabetes (PAID) questionnaire. This German study involved 372 adults with diabetes, of whom 142 had type 1 diabetes. Patients who were positive on one of the depression questionnaires subsequently participated in the Composite International Diagnostic Interview (CIDI). The BDI measures the severity and depth of depression symptoms, whereas the PAID is designed to identify negative emotional responses related to various aspects of diabetes.

In the subgroup of patients with type 1 diabetes, the prevalence of clinical depression was 30%, and a further 31% were diagnosed with subclinical depression. In the total study group, the authors found that the BDI was the most sensitive assessment method for detecting clinical depression (as defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision – ICD-10), with a good balance between sensitivity (87%) and specificity (81%), using receiver operating characteristic (ROC) analysis. This was higher than the PAID questionnaire’s ability to screen for clinical depression, with a sensitivity of 81% and a specificity of 74%. Positive predictive values for both tools were low (BDI 43% and PAID 34%), while negative predictive values were high (97% and 96% respectively). The BDI was also more sensitive than the CIDI. All methods had low sensitivity for the detecting diabetes-specific emotional problems. None of the analyses were specific to patients with type 1 diabetes (Hermanns et al 2006).

The BDI was also evaluated as a screening tool for major depression in diabetes in a United States study of 172 adults with diabetes, 59 of whom had type 1 diabetes (Lustman et al 1997). The BDI was compared with a diagnostic interview (the National Institute of Mental Health Diagnostic Interview Schedule), as outlined in the *Diagnostic and statistical manual of mental disorders* (DSM)-III-R criteria, using ROC analysis. The BDI effectively discriminated depressed participants from those that were not depressed, using the full 21-item BDI, the cognitive items alone, or the somatic items alone – although the cognitive items were more effective than the somatic items. The authors also found that a cut-off score of 16 or more provided a sensitivity of 70% and positive predictive value of 70%. They concluded that the BDI is an effective screening test for major depression in adults with diabetes.

Summary

A single study suggested that the CHQ may be useful as a screening tool in children with type 1 diabetes (Cameron et al 2003). Two studies indicate that the BDI may be useful in screening for depression in adults with either type 1 or type 2 diabetes (Lustman et al 1997; Hermanns et al 2006).

Evidence statement	
Q9.1	There is one Level II and one Level III study demonstrating the diagnostic accuracy of the BDI in a mixed population of type 1 and type 2 diabetes. There is one Level II study examining the diagnostic accuracy of the CHQ administered to the parents of children with type 1 diabetes. No evidence was identified for the performance of other psychological screening tools in type 1 diabetes.
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice points	
PP9.1.1	Regardless of whether a psychological screening tool is used, people with a suspected mental health disorder should be referred for appropriate assessment.
PP9.1.2	Consideration should be given to the practicality of using specific psychological screening tools in clinical practice (self versus interviewer or clinician administered; length; complexity), reference to more general tools or screening already undertaken, resourcing issues and labelling (as per mental health in general).
PP9.1.3	Diabetes care teams should have appropriate access to mental health professionals to support them in the assessment of psychological functioning in people with type 1 diabetes.
PP9.1.4	In children and adolescents with type 1 diabetes, assessment of developmental progress in all domains (i.e. physical, intellectual, academic, emotional and social development) is advised on a routine basis.
BDI, Beck Depression Index; CHQ, Child Health Questionnaire	

9.2 Education and psychological support programs

Question 9.2

What is the effectiveness of education and/or psychological support programs in type 1 diabetes:

- (i) on metabolic outcomes
- (ii) on psychological outcomes?

The detailed systematic review of this question is in Chapter 9 of the accompanying technical report, and the evidence matrix is in Section C9 of Appendix C

For the purpose of this review, education and psychological programs were defined as interventions that are delivered in either a group or one-on-one format, and are focused on changing either knowledge, behaviour or self-management skills; or have a psychological focus, such as coping skills, problem solving or family communication. Outcomes included in the search were metabolic (glycaemic control, severe hypoglycaemia, diabetic ketoacidosis [DKA]) and psychological (knowledge, self-management behaviours, psychosocial and quality of life [QoL]).

A total of 11 studies were included in this review (DAFNE Study Group 2002; Loveman et al 2003; Winkley et al 2006; Channon et al 2007; Viklund et al 2007; Couch et al 2008; George et al 2008; Snoek et al 2008; Amsberg et al 2009; Grey et al 2009; Ismail et al 2010). Of these, three were Level I studies. Couch et al (2008) is a comprehensive report from the Agency for Healthcare Research and Quality, evaluating the effectiveness of diabetes education programs in children and adolescents younger than 18 years. Loveman et al (2003) is a health technology assessment report on the effectiveness of diabetes self-management education in adults (including type 1 and type 2 diabetes), with a subanalysis

on results in studies of type 1 diabetes. Winkley et al (2006) is a systematic review and meta-analysis of the effect of psychological interventions in both children and adults with type 1 diabetes. These three reviews had a low risk of bias; however, the included studies were predominantly at high risk of bias. Of the eight Level II studies, six had a low risk of bias and two had a moderate risk of bias. Further details of the studies included in the systematic reviews, and characteristics of the Level II studies, are provided in the technical document.

9.2.1 Metabolic outcomes

Glycaemic control

In the most recent systematic review, the effect on HbA_{1c} of education programs for children and their families was reported in 33 randomised controlled trials (RCTs) (Couch et al 2008). HbA_{1c} levels decreased significantly in eight studies, three of which were categorised as family therapy, four as cognitive-behavioural therapy (CBT) and one as general diabetes education. In 9 studies, either the intervention group or both intervention group and control group reported a nonsignificant change in HbA_{1c}; in the remaining 16 studies, there was no difference between groups. The authors concluded that, due to the heterogeneity across the studies and the low methodological quality overall, there was insufficient evidence to determine whether any interventions were more effective than standard care for improving diabetes control. In contrast, the meta-analysis by Winkley et al (2006), which included 21 studies (10 in children and adolescents), found that HbA_{1c} was significantly reduced in those who had received a psychological intervention compared with those in the control group (absolute reduction 0.48% in children and 0.22% in adults). However, there was significant heterogeneity across studies. In the meta-analysis by Loveman et al (2003), education resulted in significant and long-lasting improvements in glycaemic control in adults with type 1 diabetes.

Loveman et al (2003) evaluated the clinical and cost effectiveness of educational interventions in adults with type 1 diabetes. Interventions that included a focus on diabetes self-management were included. Two RCTs in adults with type 1 diabetes met our inclusion criteria and both were of low quality (Terent et al 1985; Reichard et al 1996). The Stockholm Diabetes Intervention Study found significant differences between groups at all time points during follow-up to 10 years (Reichard et al 1996). However, the intervention in this study also involved the intensification of diabetes management, potentially confounding the effects of the education. The other RCT, which was small, found that formal education compared with self-monitoring of blood glucose did not improve glycaemic control (Terent et al 1985). Given that blood glucose monitoring is standard today, the applicability of these results to current management is questionable.

In the two primary studies testing the effectiveness of training in flexible intensive insulin management in adults with type 1 diabetes, one reported a significant reduction of 1% in HbA_{1c} in the intervention group at 6 months (DAFNE Study Group 2002), and the second reported no difference between groups at any time point up to 12 months' follow-up (George et al 2008). The latter study involved a brief (2.5 days) psycho-educational intervention; it is possible that the shorter duration and or nature of the intervention may explain the lack of effect on HbA_{1c}. In the three primary studies testing the effectiveness of psychological interventions, CBT reduced HbA_{1c} by about 0.5% at 48 weeks' follow-up in one study (Amsberg et al 2009), and had no effect on HbA_{1c} in two studies (Snoek et al 2008; Ismail et al 2010). However, CBT in combination with motivational enhancement therapy significantly reduced HbA_{1c} (by 0.45%) compared with usual care (Ismail et al 2010).

Severe hypoglycaemia

In the systematic review by Couch et al (2008), three of the six included RCTs reported a significant effect of an intervention on rates of severe hypoglycaemia in children and adolescents. One of the RCTs used a general diabetes education intervention (Svoren et al 2003), one a CBT intervention (Grey et al 2000), and one a skills-based intervention (Nordfeldt and Ludvigsson 2002). The authors concluded that there was no clear evidence that educational interventions had an effect on short-term complications (Couch et al 2008). However, they noted most studies did not have high enough rates of DKA to show significant differences. Furthermore, it is possible that both standard care and standard diabetes education reduce the incidence of hypoglycaemia, making it difficult to demonstrate differences across these educational interventions. One systematic review in adults reported hypoglycaemia as an outcome; however, the authors did not specifically report results for severe hypoglycaemia (Loveman et al 2003). The two primary studies in which severe hypoglycaemia was reported as an outcome both found no significant effect on the rate of severe hypoglycaemia (DAFNE Study Group 2002; George et al 2007).

Diabetic ketoacidosis

In the systematic review by Couch et al (2008), one RCT reported a significant effect of CBT on rates of DKA (Grey et al 2000) and one RCT found no effect. Only one of the included studies by Loveman et al (2003) reported DKA as an outcome, and this study found no difference between the intervention and control groups (Terent et al 1985). It is likely, however, that these studies were not sufficiently powered to detect a between-group difference in rates of DKA.

9.2.2 Psychological outcomes

Knowledge

The systematic review by Couch et al (2008) included 11 RCTs in children and adolescents that assessed the impact of interventions on knowledge. The interventions included general diabetes education (n=5), CBT (n=3) and diabetes camps (n=3). The results of studies were inconsistent, with three studies of low quality reporting a statistically significant increase in knowledge, four studies (one of low quality and three of moderate quality) reporting knowledge gains that were not statistically significant, and four studies (three of low quality and one of high quality) reporting no change. In the one study in adults reporting knowledge as an outcome, a diabetes knowledge test demonstrated no significant change as a result of an educational intervention, the Brief Intervention in Type 1 diabetes, Education for Self-efficacy (BITES) (George et al 2008).

Self-management behaviours

There were 15 RCTs from the review by Couch et al (2008) that assessed self-management and regimen adherence in young people with type 1 diabetes; one study of moderate quality and seven of low quality reported significant improvement in self-management in the intervention group. Successful interventions included general diabetes education (n=3), CBT (n=3) and family therapy (n=2). The remaining studies did not show a significant change.

Psychosocial

There were 21 RCTs from the review by Couch et al (2008) that examined one or more psychosocial outcomes in young people with type 1 diabetes, including family or social relationships, family or social support, social skills, coping, self-perception, self-efficacy, stress, depression and anxiety. The authors concluded that diabetes education was effective in improving several psychosocial outcomes; however, study quality was generally low and

there was considerable heterogeneity across interventions, time points and measures used. The meta-analysis by Winkley et al (2006) reported a significant reduction in psychological distress with psychological therapy in children and adolescents (pooled estimate -0.46 , 95% confidence interval [CI]: -0.83 to -0.10 , $p=0.013$), based on four studies, while in adults there was some evidence for a reduction in psychological distress with therapy, but this did not reach statistical significance (pooled estimate -0.25 , 95%CI: -0.51 to 0.01 , $p=0.059$).

Primary studies in children, adolescents and adults also provide evidence for an effect of educational and psychological interventions on psychosocial outcomes. Motivational interviewing was associated with significant benefits on various psychosocial measures in adolescents after 12 months, including more positive wellbeing, less depression and anxiety, and differences in personal models of illness (Channon et al 2007). In the two studies of adults that tested the effectiveness of educational training, one reported a beneficial effect of flexible intensive insulin management on dietary freedom (DAFNE Study Group 2002), and the other found that the brief educational intervention (BITES) led to significant improvements in treatment satisfaction and empowerment for up to 12 months, but no significant changes on the Illness Perception Questionnaire and Hypoglycaemia Fear Scale (George et al 2008). In three RCTs examining psychological interventions in adults, CBT had a significant effect on wellbeing, diabetes-related distress, frequency of blood glucose level testing, avoidance of hypoglycaemia, perceived distress, anxiety and depression in one study (Amsberg et al 2009); CBT had no effect on psychosocial outcomes in a second study (Ismail et al 2010); and in the third study, which compared CBT with blood glucose awareness training, both interventions resulted in fewer depressive symptoms during 12 months of follow up (Snoek et al 2008).

Quality of life

The systematic review by Couch et al (2008) reported that the results of the included RCTs were mixed, and concluded that there was limited evidence for the effect of educational interventions on QoL. The RCT by Laffel et al (2003) found no difference in QoL scores between the family therapy group and control group. One study of moderate quality found that adolescents who received coping skills training, together with intensive diabetes management, experienced less negative impact on QoL compared to controls (Grey et al 2000). In the RCT by Channon et al (2007), there was a significant improvement in QoL (as measured by the diabetes QoL) for the group receiving motivational interviewing in measures of satisfaction, impact of diabetes and worries.

None of the RCTs in adults reported by Loveman et al (2003) used validated QoL measurement tools; therefore, results were not reported in this review.

9.2.3 Summary

This systematic review (Question 9.2) examining the effectiveness of education or psychological interventions on (i) metabolic outcomes (e.g. reducing HbA_{1c}, severe hypoglycaemia and DKA, and (ii) improving psychological outcomes, is based on three Level I studies of low risk of bias, and eight Level II studies, six of which were of low risk of bias and two of moderate risk of bias. The studies included in the three Level I studies were predominantly of high risk of bias.

In children and adolescents, the effects of educational or psychological interventions were heterogeneous, and results were inconsistent in their effect on HbA_{1c}, severe hypoglycaemia, DKA, knowledge, self-management behaviours and psychological outcomes. Two studies examining refinements to intensive therapy education suggested that

educational interventions might increase the effects of intensive diabetes management on reducing HbA_{1c}. A pooled analysis of 10 studies found a 0.5% reduction in HbA_{1c} following psychological interventions, but with significant heterogeneity in the study results. Psychological distress was significantly lower following psychological interventions in children and adolescents.

In adults, self-management education significantly lowered HbA_{1c} (by 0.5–1.0%) when delivered in conjunction with intensive diabetes management, but this was not a consistent finding, reflecting heterogeneity of interventions and study quality. Specific psychological interventions (e.g. CBT) also significantly reduced HbA_{1c} (by about 0.5%), whereas a pooled analysis of psychological interventions found no significant effect on HbA_{1c}, with significant heterogeneity reported. Self-management education in the context of intensive insulin management consistently resulted in significant improvements in a number of psychological outcomes, including QoL.

One primary study was carried out in Australia, the rest were conducted in countries with a well-established health-care system; thus, the results are applicable to the Australian health-care system.

9.2.4 Cost and cost effectiveness of different education programs

This section was not systematically reviewed. Information on cost effectiveness was addressed in one systematic review by Loveman et al (2003), in which the authors reported that economic evaluations comparing education with usual care or other educational interventions were not identified. Cost analysis and information from sponsor submissions indicated that, where costs associated with patient education were in the region of 500–600 pounds sterling per patients, the benefits over time would have to be very modest to offer an attractive cost-effectiveness profile. The other two systematic reviews did not report cost effectiveness (Winkley et al 2006; Couch et al 2008).

Evidence statement	
Q9.2	<p>There is some evidence from Level I and II studies for a beneficial effect of psychological support programs and education on glycaemic control in children and adolescents. There is insufficient evidence to identify a particular intervention that is more effective than standard care to improve glycaemic control.</p> <p>There is Level I and II evidence that educational or psychological interventions improve some psychological outcomes, including psychological distress and self-management behaviours in young people with type 1 diabetes.</p> <p>The evidence base shows that the intensified education programs delivered in Reichard et al (1996) and the DAFNE Study Group (2002) are associated with reductions in HbA_{1c} compared with usual care in adults. However, the intensified education programs delivered in the BITES program and by Terent et al (1985) were not associated with reductions in HbA_{1c} compared with usual care.</p> <p>There is Level II evidence that educational and psychological interventions improve some psychological outcomes (including psychological wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression) in adults.</p>
Recommendation	
R9.2	<p>Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).</p>

Practice points	
PP9.2.1	Educational and psychological interventions should be culturally, developmentally and age appropriate.
PP9.2.2	The multidisciplinary diabetes health-care team should aim to maintain consistent contact with people with diabetes and their families or carers.
PP9.2.3	It is important for the multidisciplinary diabetes team to provide preventive interventions for patients and families (include training parents in effective behaviour-management skills) at key developmental stages, including after diagnosis and before adolescence. The aim of these interventions is to emphasise appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control(Delamater 2009).
PP9.2.4	Diabetes care teams should have appropriate access to mental health professionals to support them in the delivery of psychological support(NICE 2010).
PP9.2.5	Flexible intensive insulin therapy programs, such as DAFNE, aim to provide dietary freedom for people with type 1 diabetes
BITES, Brief Intervention in Type 1 diabetes, Education for Self-efficacy; DAFNE, dose adjustment for normal eating; HbA _{1c} , glycated haemoglobin	

10 Nutrition

Nutritional management is fundamental to diabetes care and education. Dietary recommendations for individuals with type 1 diabetes are based on healthy eating recommendations suitable for all children and adults (there are no specific recommendations for type 1 diabetes), and thus for the whole family. Nutritional advice should be adapted to cultural, ethnic, religious and family traditions, as appropriate. The main aims of nutritional management in type 1 diabetes are to (Smart et al 2009):

- encourage appropriate eating behaviour and healthy lifelong eating habits, while preserving social, cultural and psychological wellbeing
- encourage people to eat three nutritious meals a day, with appropriate healthy snacks (if necessary), to supply all essential nutrients and maintain a healthy weight, in association with regular monitoring of blood glucose levels
- provide sufficient and appropriate energy intake and nutrients for optimal growth, development and good health
- achieve and maintain an appropriate body mass index (BMI) and waist circumference through healthy eating and regular physical activity
- achieve a balance between food intake, metabolic requirements, energy expenditure and insulin action profiles, to attain optimal glycaemic control
- prevent and treat acute complications of diabetes, such as hypoglycaemia, hyperglycaemia and illness
- reduce the risk of microvascular and macrovascular complications
- maintain and preserve quality of life (QoL)
- develop an enabling, trusting, empathic, supportive relationship, to facilitate behaviour change and consequent positive dietary modifications

There is evidence for the nutritional requirements of young people in general; however, the evidence base for many aspects of dietary management of diabetes is limited and is often not of high quality. This chapter outlines the evidence to support carbohydrate quantification, insulin-to-carbohydrate ratios, use of the glycaemic index (GI), and modification of dietary fat and protein. These are only selected aspects of the dietary management of type 1 diabetes for which clear evidence is available and does not cover all aspects of the nutritional management of the condition. Further evidence-based information on the nutritional management of type 1 diabetes, including age group specific advice, can be found in the guidelines from the International Society for Pediatric and Adolescent Diabetes (Smart et al 2009) and the American Diabetes Association (American Diabetes Association 2008). Refer to Chapters 9–11, 16 and 20 for information regarding psychosocial disorders (including eating disorders), physical activity, hypoglycaemia and coeliac disease

People with type 1 diabetes should have access to an Accredited Practising Dietitian (APD) who is qualified to provide Medical Nutrition Therapy (MNT) and is skilled in the nutritional management of the condition. However, all team members should have a thorough understanding of the principles of nutritional management of type 1 diabetes.

10.1 Carbohydrate quantification

Question 10.1

What are the efficacy and safety of

- (i) regulating or quantifying dietary carbohydrate and
- (ii) (ii) insulin-to-carbohydrate ratios in type 1 diabetes?

The detailed systematic review of this question is in Chapter 10 of the accompanying technical report, and the evidence matrix is in Section C10 of Appendix C

The NHMRC dietary guidelines, *Nutrient reference values for Australia and New Zealand including recommended dietary intakes* (NHMRC 2006), recommend that carbohydrate intake makes up 45–65% of energy intake, predominantly from wholegrain breads and cereals, legumes, fruit, vegetables and low-fat dairy products (except for children under two years). These recommendations do not differ for people with type 1 diabetes; however, the distribution of carbohydrate intake is more important. As part of individualised advice regarding carbohydrate amount and distribution, it is important to consider usual appetite, food intake patterns, exercise, insulin regimen and energy requirements.

Carbohydrate can be regulated or quantified in different ways:

- **Consistent carbohydrate intake:** For those receiving fixed mealtime doses of insulin, this approach is used; it involves day-to-day consistency in carbohydrate intake, where a consistent intake of carbohydrate is encouraged using serves or exchange lists of measured quantities of food.
- **Flexible carbohydrate intake:** Carbohydrate counting is a meal-planning approach that focuses on improving glycaemic control and allowing flexibility of food choices. This can be achieved with individualised insulin-to-carbohydrate ratios for patients using intensive insulin therapy

In clinical practice, a number of methods for carbohydrate quantification are commonly taught, including 1 g increments, 10 g carbohydrate portions and 15 g carbohydrate exchanges.

Four Level II studies have examined carbohydrate-based interventions in type 1 diabetes. One study used a flexible low-GI diet, but did not include the use of insulin-to-carbohydrate ratios (Gilbertson et al 2003), and three studies used flexible intake of carbohydrate with adjustment of insulin based on insulin-to-carbohydrate ratios (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010). Only one study included children (Gilbertson et al 2003) and was of good quality. The results of this study are discussed in Section 10.2, below. No studies that examined flexible diet or the use of insulin-to-carbohydrate ratios in adolescents were identified.

The three studies that examined insulin-to-carbohydrate ratios were all conducted in adults receiving MDI therapy (n=446) (Kalergis et al 2000; DAFNE Study Group 2002; Scavone et al 2010), and one was of good quality (DAFNE Study Group 2002). The studies involved comprehensive education programs of which insulin-to-carbohydrate ratios were an integral part of the whole program. The DAFNE study group (DAFNE Study Group 2002) found a lower HbA_{1c} in the intervention group (8.4% vs 9.4% at 6 months, p<0.0001) compared with no change in the control group (9.3% vs 9.4%), while HbA_{1c} was not different between

groups in the other studies. QoL, measured using a validated tool was better in the intervention group than in the control group in the DAFNE study (DAFNE Study Group 2002). There were no between-group differences in weight, BMI or severe hypoglycaemia. There is some evidence to suggest an improvement in both HbA_{1c} and QoL in adults who have received education on the use of insulin-to-carbohydrate ratios to enable a liberalised carbohydrate intake.

Evidence statement	
Q10.1	Level II evidence (from three studies) shows that the use of insulin-to-carbohydrate ratios in multiple daily injection therapy reduces HbA _{1c} but has no clinically significant effect on weight, QoL or severe hypoglycaemia.
Recommendation	
R10.1	Matching of mealtime insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).
Practice points	
PP10.1.1	An individualised insulin to carbohydrate ratio should be used for individuals using CSII and may be used in those on multiple daily injection therapy as part of a comprehensive education program.
PP10.1.2	Adjusting insulin with carbohydrate quantity has the potential to improve QoL and increase flexibility in food intake in people with type 1 diabetes. However, regularity in meal routines remains important for optimal glycaemic control.
PP10.1.3	Advice on carbohydrate quantity and distribution should take into account an individual's energy requirements, previous dietary and eating patterns, activity levels and insulin regimen.
PP10.1.4	Advice on carbohydrate quantification should be given within the context of a healthy diet to ensure that overall nutritional needs are being met. In contrast, focussing solely on carbohydrate can lead to poor food choices, carbohydrate avoidance and/or insulin omission.
PP10.1.5	Matching insulin to carbohydrate requires comprehensive education in accurate carbohydrate counting, which should be provided by a dietitian experienced in this area.
PP10.1.6	Day-to-day consistency in carbohydrate intake is important for patients who are on fixed insulin regimens.
CSII, continuous subcutaneous insulin infusion; HbA _{1c} , glycated haemoglobin; QoL, quality of life	

10.2 Glycaemic index

Question 10.2

What are the efficacy and safety of low glycaemic index or high-fibre diets in type 1 diabetes?

The detailed systematic review of this question is in Chapter 10 of the accompanying technical report, and the evidence matrix is in Section C10 of Appendix C

GI is a ranking of foods based on their acute glycaemic impact compared to the reference standard glucose (Wolever et al 1991). Carbohydrates with a low GI result in a slower and more gradual rise in blood glucose levels, and reduce the postprandial glycaemic response compared to carbohydrates with a higher GI. Lower GI food sources include wholegrain breads; legumes; pasta; wholegrains such as oats, barley and quinoa; many fruits (temperate, citrus, most stone fruit and berries); and dairy foods. Many factors may influence a food's glycaemic response; however, the ranking of foods on the basis of their GI value is generally consistent (Wolever et al 1991).

Glycaemic load (GL) is another method of predicting the postprandial blood glucose response, which takes into account both the GI of the food and the portion size (Salmeron et al 1997). Low-GL diets are usually relatively higher in dietary fibre. There has been no assessment of the efficacy of low-GL diets in children, adolescents or adults, nor have any RCTs exclusively addressed high fibre intake.

A recent systematic review of 11 randomised controlled trials (RCTs) assessed the effects of low-GI or low-GL diets on glycaemic control in people with diabetes (Thomas and Elliott 2009). Four RCTs involved 186 patients with type 1 diabetes (Collier et al 1988; Fontvieille et al 1992; Giacco et al 2000; Gilbertson et al 2001); of these, two were paediatric studies, including one RCT of 104 Australian children aged 8–13 years (Gilbertson et al 2001). Two studies reported HbA_{1c} as an outcome — one that involved children (Gilbertson et al 2001) and the other adults (Giacco et al 2000); pooled analysis showed a significant difference in HbA_{1c} in the low-GI group versus the conventional or high-GI group (weighted mean difference [WMD] –0.5%, 95% confidence interval [CI]: –0.9 to 1.0, p=0.02).

In the Australian study (Gilbertson et al 2001), the intervention group was prescribed a flexible low-GI diet, and the control group received a fixed quantity of dietary carbohydrate. At 12 months, children in the low-GI group had lower HbA_{1c} levels than those in the carbohydrate-exchange group (8.1% vs 8.6%, p=0.05). The study was conducted at a time when conventional insulin therapy was used more frequently in children with type 1 diabetes and before continuous subcutaneous insulin infusion (CSII) was widely used. Therefore, the results of this study may not be directly applicable to treatment regimens such as CSII and multiple daily injections that are currently more commonly used in children with type 1 diabetes.

Hypoglycaemia was reported in two studies (Giacco et al 2000; Gilbertson et al 2001); the mean rate of any hypoglycaemic event per month was lower in adults randomised to a low-GI diet (0.7 vs 1.5 in the high-GI group, p<0.01) (Giacco et al 2000).

Improved QoL was reported for both children and parents in one study (Gilbertson et al 2001), based on a higher rate of diabetes never limiting the type of family activities pursued (53% vs 27%, p=0.02).

Low GI diets also improve blood fats in people with type 1 diabetes (Buyken et al 2001) however, this current systematic evidence based review only examined the effects on glycaemic control, weight management and hypoglycaemic events. For individuals using CSII therapy, limited data indicate that use of the dual-wave bolus with a low GI meal may assist in optimising postprandial glycaemia (O'Connell et al 2008).

Evidence statement	
Q10.2	Level I evidence shows that a low GI diet has a beneficial effect on glycaemic control in adults and children. There is insufficient evidence to determine the effect of low-GI diets on body mass index, weight, severe hypoglycaemia or QoL in children, adolescents or adults with type 1 diabetes.
Recommendation	
R10.2	Individuals with type 1 diabetes should be educated on low-GI diets (Grade A).
Practice point	
PP10.2.1	GI should not be used in isolation, but with a method of carbohydrate quantification or regulation.
PP10.2.2	High GI food choices combined with low GI food choices can lower the glycaemic impact of a meal.
PP10.2.3	Where possible, high GI food choices should be substituted with moderate or low GI choices.
PP10.2.4	Food choices should also consider other nutritional aspects in addition to GI, with a focus on lower fat, higher fibre, nutrient-dense foods.
GI, glycaemic index; QoL, quality of life	

10.3 Protein

Question 10.3

What are the efficacy and safety of a high protein diet in type 1 diabetes?

The detailed systematic review of this question is in Chapter 10 of the accompanying technical report, and the evidence matrix is in Section C10 of Appendix C

Nutritional guidelines for the Australian population recommend that protein should comprise up to 25% of total daily energy intake (NHMRC 2006). Sources of vegetable protein, such as legumes, should be encouraged. Sources of animal protein also recommended include fish, lean cuts of meat and low-fat dairy products.

In the presence of persistent microalbuminuria or established nephropathy, excessive protein intake may be detrimental to renal function (NHMRC 2006). There is also evidence that vegetable or soy protein may be preferable to animal protein, particularly red meat, with respect to reducing the progression of renal disease (Robertson et al 2009c). However, the evidence base for modification of other outcomes in type 1 diabetes is limited.

One systematic review of eight RCTs examined the effect of low-protein diets (0.6-0.8g/kg body weight) in adults with type 1 or 2 diabetes-related renal diseases. Four studies involved 70 adults with type 1 diabetes (Pan et al 2008). In this subgroup, change in HbA_{1c} from baseline to study end did not differ between the intervention and control groups (WMD: 0.04%, 95%CI: -0.53 to 0.61, I²=0%, p=0.89). Other outcomes relevant to diabetes (e.g. BMI, weight, QoL and rates of severe hypoglycaemia) were not examined in the systematic review.

There is no Level I or II evidence for the efficacy and safety of low-protein diets in children and adults with type 1 diabetes and normal renal function. There is no evidence for the efficacy and safety of high-protein diets versus normal diets in children and adults with type 1 diabetes and normal renal function.

Evidence statement	
Q10.3	There is insufficient evidence to determine the effect of modifying protein intake in individuals with type 1 diabetes.
Recommendation	
There was insufficient evidence to make a recommendation.	
Practice points	
PP10.3.1	High-protein/low-carbohydrate diets in children and adolescents may have deleterious effects on growth.
PP10.3.2	High-protein diets, particularly those based on animal protein or red meat, may lead to progression of diabetic nephropathy. Reducing protein intake to levels consistent with the recommended dietary intakes or replacing red meat with vegetable or soy protein may help to reduce the progression of nephropathy.
PP10.3.3	Restricting carbohydrate intake may affect the nutritional adequacy of the diet and may cause hypoglycaemia if insulin therapy is not adjusted accordingly.
PP10.3.4	High-protein, low carbohydrate diets result in ketosis, which may affect blood glucose control and result in dehydration, lethargy and loss of lean body mass.

10.4 Fat

Question 10.4

What are the efficacy and safety of modifying dietary fat intake in type 1 diabetes?

The detailed systematic review of this question is in Chapter 10 of the accompanying technical report, and the evidence matrix is in Section C10 of Appendix C

Nutritional guidelines for the Australian population recommend that fat should comprise about 20–35% of total daily energy intake (NHMRC 2006). The recommended targets for fat intakes do not differ for people with diabetes; however, studies have shown that children, young people and adults with diabetes consume fat and saturated fat above dietary recommendations (Helgeson et al 2006; Overby et al 2007; Snell-Bergeon et al 2009). Recent consensus guidelines for nutritional management of type 1 diabetes (Smart et al 2009) recommend the following composition of dietary fat:

- less than 10% of energy from saturated fat and trans fats
- less than 10% of energy from polyunsaturated fat
- more than 10% of energy from monounsaturated fat.

Five Level II studies examined modification of dietary fat intake in 118 people with type 1 diabetes (Donaghue et al 2000; Georgopoulos et al 2000; Strychar et al 2003; Rosenfalck et al 2006; Strychar et al 2009). Four were RCTs or crossover studies in adults, and one was a randomised parallel study in 25 adolescents (Donaghue et al 2000). Four studies assessed the effect of high monounsaturated fat diets (up to 40% of energy from total fat with 20% from monounsaturated fat) and one randomised crossover study in 10 adults examined the effect of a low-fat (25%) isoenergetic diet (Rosenfalck et al 2006).

In the four studies that examined a high monounsaturated fat diet, there was no difference in HbA_{1c} between the intervention and control groups. One study reported a statistically

significant, but modest, increase in weight (2%) in the intervention group (Strychar et al 2009).

In the study that examined a low-fat diet, insulin sensitivity improved significantly in the intervention group, but there was no difference in HbA_{1c}, weight or BMI (Rosenfalck et al 2006). The effect on lipid profiles was variable across the five studies. There was a significant improvement in LDL-cholesterol following the monounsaturated diet intervention in one RCT (Strychar et al 2003), and in total triglycerides (TG), very low-density lipoprotein (VLDL) TG and VLDL-cholesterol in the subgroup of participants who had adhered to required dietary targets. There were no significant differences in lipid profiles in the two other RCTs (Georgopoulos et al 2000; Strychar et al 2009).

Two studies reported low dietary adherence rates, suggesting that adherence to high monounsaturated fat diets in patients with type 1 diabetes may be poor (Donaghue et al 2000; Strychar et al 2003). Furthermore, it is likely that diets high in monounsaturated fats are difficult to adhere to in the context of an Australian diet. QoL and severe hypoglycaemia were not measured as outcomes in any of these studies.

No RCTs have been published examining the effect of modifications of other types of dietary fat (saturated and polyunsaturated) in people with type 1 diabetes.

Evidence statement	
Q10.4	Level II evidence (from one, good-quality study, small sample size) shows that, in nonobese adults with well-controlled, uncomplicated type1 diabetes, a diet high in monounsaturated fats can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides and VLDL-cholesterol. There is insufficient evidence to determine any effect on weight, body mass index, quality of life and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes.
Recommendation	
R10.4	Diets high in monounsaturated fats should not be used routinely in type 1 diabetes (Grade C).
Practice points	
PP10.4.1	Advice on fat intake should include focussing on reducing saturated and trans fat intake, to reduce the risk of cardiovascular disease.
PP10.4.2	Substitution of saturated and trans fats with monounsaturated or polyunsaturated fats should be encouraged.
PP10.4.3	Education on carbohydrate quantification should discourage consumption of high-fat foods, particularly packaged snacks.
PP10.4.4	Advice to lower energy intake, specifically total fat intake, should be given to people with type 1 diabetes who are overweight or obese, or who are at risk of overweight or obesity.
LDL, low density lipoprotein; VLDL, very low density lipoprotein	

11 Exercise

11.1 Modification of Insulin type, dose and mode of delivery with exercise

This chapter was not systematically reviewed and as such, no recommendations or practice points are made. The narrative contains information from contemporary guidelines developed by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Robertson et al 2009b) and other references, including primary studies. The grading of evidence used in the ISPAD guidelines is shown in Chapter 2, Section 2.2.3 (Table 2.2).

Physical activity is an expected part of daily activity; it is important for cardiovascular and metabolic fitness, and general wellbeing (Laaksonen et al 2000; D'hooge et al 2010). Incidental daily physical activity can generally be managed in a person with type 1 diabetes, and does not pose an unexpected major caloric deficit (Robertson et al 2009b). In contrast, structured bouts of physical activity (as exercise) do require planning. There are well-known cases of elite athletes with type 1 diabetes, indicating that type 1 diabetes is not an impediment to optimal performance during exercise (Robertson et al 2009b).

A number of studies in people with type 1 diabetes have shown that structured exercise does not improve chronic glycaemic control, whereas blood glucose levels may be acutely unstable at the time of exercise (Ligtenberg et al 1999; Rabasa-Lhoret et al 2001; Särnblad et al 2005). The main concern with exercise in people with type 1 diabetes is that hypoglycaemia or possibly hyperglycaemia, may be precipitated during or after the exercise (Tuominen et al 1995). Exercise consumes energy and improves insulin sensitivity; thus, increased carbohydrate intake, reduced insulin dosage, or a combination of the two are generally required around the time of the exercise, to minimise the risk of immediate (Rabasa-Lhoret et al 2001) or delayed hypoglycaemia (McMahon et al 2007). Exercise-induced hypoglycaemia is especially likely during exercise that is of long duration (>60 minutes) or persistent and intense (Robertson et al 2009b). In contrast, in different clinical settings, exercise may exacerbate or cause metabolic instability in the form of acute hyperglycaemia (Mitchell et al 1988).

The profile of blood glucose response to any type of exercise is difficult to predict in different people with type 1 diabetes (Robertson et al 2009b). However, an initial approach using some guiding principles may be used to help keep blood glucose levels reasonably safe during exercise. Subsequently, a more personalised and detailed plan can be developed. This involves the person with type 1 diabetes carefully documenting their initial exercise strategy – including exercise type, intensity and timing – relative to meals and related exercise insulin regimen chosen, carbohydrate intake and blood glucose profile (Toni et al 2006; Robertson et al 2009b; Ambler and Cameron 2010).

In people with established end-organ diabetes complications, certain types of exercise may be contra-indicated. People with significant complications such as unstable CHD or severe diabetic foot or eye disease should receive medical care and then carefully planned, individualised physical activity programs once these complications have been stabilised. For example, in a person with dense peripheral neuropathy, exercise such as swimming, upper body exercises, or stationary cycling may be preferred to those requiring greater shear stress on the feet such as road walking or running or competitive ball sports.

11.2 General principles in initial exercise planning

11.2.1 Carbohydrate requirement

The intensity and duration of the exercise will affect the amount of energy consumed due to the exercise, and thus the estimated amount of carbohydrate required. Data are readily accessible to estimate the calories (including carbohydrate) expended in differing activities (Pendergast et al 2010). For example, in a child weighing 40 kg, 30 minutes of basketball will consume an estimated 120 kilocalories (508 kJ) of carbohydrate (Robertson et al 2009b).

More predictable blood glucose responses to exercise will occur in a person who has ongoing cardiovascular fitness, has better controlled HbA_{1c} levels, and undertakes the exercise in a set routine, including in its timing, each day or every second day (Robertson et al 2009b).

The type of exercise, and its timing relative to meals and administration of rapid-acting insulin is likely to affect the approach to modifying carbohydrate intake and insulin dosage. Carbohydrate and insulin therapy may be modified following some of the guidelines below (Toni et al 2006).

- **Ensure adequate energy stores before exercise.** A meal containing carbohydrates, fats and protein should be consumed about 3–4 hours before exercise, to maximise endogenous energy stores. Glycogen stores can be optimised if carbohydrate is consumed; for example, as a beverage with 1–2 g carbohydrate/kg body weight (Robertson et al 2009b).
- **Supplemental carbohydrate.** If supplemental carbohydrate is taken during exercise (which is usually required if the exercise lasts more than 30 minutes), 6% oral solutions with rapidly absorbed (high glycaemic index [GI]) carbohydrate appear to be most efficient (Riddell and Iscoe 2006). If the insulin dosage is not reduced, then the carbohydrate intake amount should be matched as far as possible with the predicted requirement of carbohydrate. As a guide, during the time of peak insulin action, the typical amount of carbohydrate required is 1.0–1.5 g of carbohydrate per kg of body weight per hour (Riddell and Iscoe 2006).
- **Reduce insulin doses before exercise.** If the planned exercise is to be more than 60 minutes in duration, then a reduction in bolus insulin using insulin changes as described above, combined with progressive supplemental carbohydrate every 30–40 minutes, is indicated (Robertson et al 2009b).

Detailed guidelines for carbohydrate intake in children and adolescents, varying with the duration and intensity of exercise, are available (Ambler and Cameron 2010).

11.2.2 Insulin therapy

Multiple daily injection and insulin pump (continuous subcutaneous insulin infusion [CSII]) therapy-based regimens provide the greatest flexibility in insulin adjustment for exercise and is the most effective means of assisting in weight loss with exercise. The highest risk time for initial hypoglycaemia after exercise using rapid acting insulin analogues is 40–90 minutes, and for regular (soluble) insulin, is 2–3 hours (Tuominen et al 1995). Therefore, the dose of insulin that is acting at the time of the exercise (especially rapid or short acting) may need to be reduced. Suggested changes to insulin doses based on the time of day and duration of exercise are outlined below and are only recommended in patients who generally have good metabolic control:

- **Exercise performed early in the morning, before breakfast:**
 - reduce the previous evening basal (intermediate or long-acting) insulin dose by 20–50%
 - reduce the pre-breakfast bolus (rapid-acting) insulin dose after exercise by 30–50%
 - reduce the evening dose of basal insulin on the day of exercise
- **Exercise performed in the postprandial phase:**
 - preferably delay exercise until at least 1–2 hours after the meal
 - reduce the pre-meal bolus insulin dose by 20–75%, related to duration and intensity of exercise
- **Prolonged exercise:**
 - reduce the pre-meal bolus insulin dose by 30–50% if exercise lasts up to 4 hours; for all-day exercise, reduce all meal bolus doses across the day by 30–50%
 - reduce the previous evening basal insulin by 50%, and the basal insulin dose by 10–20% up to 24 hours after all-day exercise, such as walking
- **Intermittent high-intensity exercise (team sports):**
 - reduce the pre-meal bolus insulin by 70–90% if exercise commences within 1–3 hours of the meal

For CSII therapy, decrease the basal rate by 30–50% for the duration of the exercise; and, if exercise is planned, reduce the basal rate for 1–2 hours before exercise. Alternatively, CSII may be suspended for up to 2 hours. Consider supplemental bolus insulin either before or 1 hour into exercise. In either case, a reduction in the overnight basal rate may also be needed by 20–30% or sometimes more, after vigorous and prolonged exercise.

11.2.3 Glycaemic control

Suboptimal glycaemic control with HbA_{1c} levels above 7.5% can reduce aerobic exercise capacity, and increase fatigue rate. Thus, reasonably good chronic glycaemic control is desirable to aid exercise capacity (Komatsu et al 2005).

Situations that may lead to severe hyperglycaemia around the time of the exercise, rather than hypoglycaemia in response to exercise, include (Mitchell et al 1988; Robertson et al 2009b):

- a person being insulin deficient before exercise
- the intensity of the exercise being repeated and of high intensity, such as that above maximum oxygen uptake of 80%
- the exercise causing mainly anaerobic metabolism.

These situations will lead to release of high levels of noradrenaline. In addition, excessive emotional stress or excess carbohydrate intake can contribute to hyperglycaemia related to exercise (Robertson et al 2009b). If the blood glucose level is above 14 mmol/L not directly after eating, then it is generally recommended that exercise not be undertaken (Robertson et al 2009b). In such cases, if the person feels unwell or if blood glucose rises above 15 mmol/L, then blood or urine ketones should be assessed as part of sick day management as described in Chapter 17.3.

11.3 Fine tuning an initial exercise regimen through monitoring

Once an initial exercise plan has been developed with the person with diabetes, it is useful to carefully monitor and document the blood glucose profile during and after exercise episodes, to help in fine tuning the regimen (Toni et al 2006). This iterative approach allows progressive documentation of reproducibility of the blood glucose response with exercise.

Further strategies to prevent hypoglycaemia related to exercise and its severity due to exercise are outlined below.

11.3.1 Sprinting

A recent publication from Australian data has indicated that a 10-second sprint at the end of a bout of exercise can help to prevent hypoglycaemia some 2 hours after the exercise (Bussau et al 2007). This preventive role appears to be the case for certain types of exercise, such as consistent, moderate-intensity aerobic physical activity.

11.3.2 Preventing nocturnal hypoglycaemia

Severe, nocturnal hypoglycaemia is more prone to occur up to 24 hours after a bout of at least moderate physical activity undertaken for at least 1 hour (Robertson et al 2009b). In one study in adolescents, the rate of nocturnal hypoglycaemia was about double (48% of participants had events) on nights of exercise days compared with nights when no exercise had been undertaken during the day (Tsalikian et al 2005). The effect appears to be mainly due to increased insulin sensitivity through induction of glucose transporter type 4 in skeletal muscle (Gulve and Spina 1995). In addition, data indicate that counter-regulatory hormone and autonomic nervous system responses to hypoglycaemia may be blunted following a significant bout of exercise (Sandoval et al 2004).

The following strategies have been suggested to help prevent nocturnal hypoglycaemia due to exercise undertaken within the past 24 hours:

- reduce the long-acting insulin dose overnight after the exercise undertaken that day; for example, the dose of long-acting insulin could be reduced from 10–20% (Taplin et al 2010), and in some cases up to 50% (Toni et al 2006)
- basal insulin rates overnight in CSII may need to be reduced by 20-30%.
- ensure blood glucose is above 7 mmol/L before going to bed (Whincup and Milner 1987; Tansey et al 2006)
- always consume at least 10–15 g carbohydrate before bed after a day of exercise (Whincup and Milner 1987), preferably as a low-GI food or with a mixed meal, such as a glass of milk, to aid a slow but persisting rate of glucose absorption into the blood stream
- in higher risk settings after days of unusually intense or long-duration physical activity, consider setting the bedroom alarm clock in the early morning hours to check blood glucose at those times, and to supplement with carbohydrate as required
- monitor blood glucose continuously, to help in recognising asymptomatic hypoglycaemia (monitoring can include both retrospective and real-time systems) (Riddell and Perkins 2009); real-time monitoring systems often have a hypoglycaemia alarm triggered by a threshold blood glucose level, to help avoid severe hypoglycaemia.

11.3.3 Hypoglycaemia and recreational sport

Scuba diving is currently contraindicated in people with type 1 diabetes, because of the complications posed by hypoglycaemia occurring under deep water, and the difficulty in monitoring blood glucose in that setting (Australian Diabetes Society 1994). The sport is conditionally supported for some people in some developed countries, and there are highly specific guidelines for it to be undertaken (Lormeau et al 2005). However, scuba diving can be associated with mishap in people with type 1 diabetes, and it can cause major swings in blood glucose levels (Dear Gde et al 2004). Other studies have shown that, in people without hypoglycaemia unawareness or major diabetes complications, scuba diving can be safe (Edge et al 2005). The field is evolving (Lormeau et al 2005), including in blood glucose monitoring technology underwater (Adolfsson et al 2009; Bonomo et al 2009; Pollock 2009). It may eventuate that Authorities in Australia will support conditional approval for people with type 1 diabetes to scuba dive on a case-by-case assessment basis.

11.3.4 Preventing hypoglycaemia in children

Parents and carers of children must ensure ready access to carbohydrates, particularly in young children, to help prevent hypoglycaemia related to physical activity. During increased physical activity beyond the usual amount, the carer or parent should be highly suspicious that hypoglycaemia may occur. At school and sporting activities, it is particularly important for teachers or others responsible for the child with diabetes to be aware of the risk of hypoglycaemic episodes with exercise, and they should know how to recognise and treat such episodes.

In a research setting, the β 2 agonist terbutaline taken orally at bedtime prevented nocturnal hypoglycaemia related to exercise in children with type 1 diabetes; however, terbutaline often induces hyperglycaemia and is not recommended (Taplin et al 2010). Appropriate oral carbohydrate and glucagon should be ready accessible to the primary carer, as required, to help prevent or treat severe hypoglycaemia episodes. Treatment of hypoglycaemia is addressed in Chapter 16.

11.3.5 Preventing hypoglycaemia in adolescents and adults when exercise is combined with alcohol

Moderate or large consumption of alcohol is well known to cause delayed hypoglycaemia after 6–12 hours (Plougmann et al 2002; Cryer et al 2003). Alcohol reduces gluconeogenesis (Robertson et al 2009b), and particular care should be taken when it is combined with exercise; for example, at ‘big nights out’ or dance parties. In these situations, severe hypoglycaemia may also be mistaken for effects of alcohol, or other mood and mind-altering drugs. Severe hyperglycaemia and diabetic ketoacidosis may also occur in these settings (Lee et al 2009). With due care in diabetes self-management, outcomes in managing blood glucose during social events – including those involving physical activity – may be positive (Ramchandani et al 2000). Specific advice to reduce the risk of hypoglycaemia and adverse outcomes includes:

- eat carbohydrate beforehand, during the period of drinking, and afterwards
- consider reducing overnight insulin to avoid overnight hypoglycaemic episodes after drinking alcohol
- arrange for a responsible person to if possible stay overnight and/or wake the person the next morning at an appropriate time, to see that all is well and that the person is easily rousable.

12 Complementary and alternative medicines

A range of complementary medicines – herbal medicines, antioxidants, vitamins and heavy metals are used by people with diabetes, although most clinical research addressing complementary and alternative medicines (CAM) has been performed in people with type 2 diabetes (Yeh et al 2003). A systematic review examined the effectiveness of CAM in achieving metabolic targets in type 1 diabetes.

12.1 Effectiveness, cost and cost effectiveness of complementary therapies and alternative medicines

Question 12.1

(i) (interventional)

What is the effectiveness of complementary and alternative medicines at achieving metabolic targets?

(ii) (interventional cost effectiveness)

What are the costs and cost effectiveness of complementary and alternative medicines at achieving metabolic targets?

The detailed systematic reviews of these questions are in Chapter 12 of the accompanying technical report, and the evidence matrixes are in Section C12 of Appendix C

Four systematic reviews met the inclusion criteria in examining complementary medicines in type 1 diabetes (Pozzilli et al 1996; Yeh et al 2003; Pilkington et al 2007; Baker et al 2008). The studies captured by these Level I studies were supplemented by Level II studies that were published after the Level I studies (Pozzilli et al 1996; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Manuel et al 2004; Pena et al 2004; Engelen et al 2005; Pitocco et al 2006; Giannini et al 2007; Huang and Gitelman 2008). A number of trials studied the effect of herbs (Sharma et al 1990; Serraclara et al 1998) and vitamin supplements (Crinò et al 2004; Manuel et al 2004; Engelen et al 2005; Giannini et al 2007).

12.1.1 Effectiveness of complementary and alternative medicines

Glycaemic control was an outcome measure in 10 studies (Pozzilli et al 1996; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pena et al 2004; Pitocco et al 2006; Altschuler et al 2007; Giannini et al 2007; Huang and Gitelman 2008). All the included studies found no difference in glycated haemoglobin (HbA_{1c}). A meta-analysis conducted by Pozzilli et al (1996), which looked at nicotinamide treatment in patients with recent-onset type 1 diabetes, reported no differences in HbA_{1c} values between nicotinamide and control patients.

Insulin dose was an outcome measure in nine studies (Sharma et al 1990; Pozzilli et al 1996; Serraclara et al 1998; Visalli et al 1999; Ludvigsson et al 2001; Crinò et al 2004; Pitocco et al 2006; Altschuler et al 2007; Huang and Gitelman 2008). Of these, eight studies found no difference in overall insulin requirement. The study by Serraclara et al (1998) showed a reduction in insulin dose (12% lower in the intervention group) (no raw data were provided in the study), and there was a decline in mean capillary glycaemia ($p < 0.05$). However, this

study was graded as being of poor quality (Yeh et al 2003). The meta-analysis of 10 randomised controlled trials (RCTs) by Pozzilli et al (1996) also reported no difference in insulin dose required between nicotinamide and control patients.

Lipid targets were an outcome in two studies, both of which examined the effect of vitamin E compared to conventional treatment (Manuel et al 2004; Engelen et al 2005). A combination of vitamin E plus fenofibrate or atorvastatin did not improve lipid levels compared to fenofibrate or atorvastatin alone.

Overall, adverse event rates were low in the studies.

In summary, there was no consistent efficacy of complementary and alternative therapies in type 1 diabetes with respect to the parameters studied.

12.1.2 Cost-effectiveness studies

As efficacy was not demonstrated, evidence of cost effectiveness was not found.

12.1.3 Summary

None of the 4 reviews or 13 primary studies of CAM in type 1 diabetes provided evidence for effects on glycaemic control. Similarly, there was insufficient evidence for other outcomes. The search strategy included only Level I and II studies; therefore, lower level studies at higher risk of bias were not considered. The outcome of studies using CAM may be influenced by the quality of the preparation studied; for example, in the case of herbal medicines, the part of the plant used and how it was prepared. The inclusion criteria for the studies varied, which limits the generalisability of the systematic review's findings for some outcomes. The studies were conducted in Australia and in countries with a well-developed health-care system, and are therefore applicable to the Australian health-care context.

Cinnamon was examined in only one RCT in adolescents with type 1 diabetes; however, it has been used for centuries in Chinese and Ayurvedic medicine, mostly to treat type 2 diabetes. Two main species are used: *Cinnamomum cassia*, which appears to be the preferred species; and *C. vera* or *C. zeylanicum*. The species have a similar chemical content, but with enough divergence to explain different clinical effects.

The systematic review did not include diabetes complications as an outcome, as was the case for the four Level I studies identified. However, there was one Level II study (a double-blind RCT) of gamma-linolenic acid in adults with type 1 and type 2 diabetes with distal diabetic polyneuropathy, confirmed both clinically and by objective nerve function studies. The intervention was associated with a significant improvement in sensory and motor nerve function, and in symptom score after 6 months. The study intervention, gamma-linolenic acid, is a constituent of evening primrose oil (*Oenothera biennis*).

No serious adverse events were reported in the included studies. However, CAM use was associated with deaths in children (Lim et al 2010); these deaths were ascribed to a failure to use conventional medicine in favour of a CAM therapy. There were 35 other reports of adverse events associated with CAM use in children. In one case, naturopathy for diabetes and a reduction in insulin dose was associated with symptomatic hyperglycaemia.

Evidence statement	
Q12.1	<p>There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon.</p> <p>All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes.</p> <p>There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.</p>
Recommendation	
R12.1	CAM should not be used in type 1 diabetes to target metabolic outcomes (Grade C).
Practice points	
PP12.1	Clinicians should ask people about CAM in a nonjudgmental way, and document their use.
PP12.2	People with type 1 diabetes should be aware that there is a lack of evidence for the effectiveness of CAM.
PP12.3	While there is evidence for a low rate of adverse events due to CAM usage, the possibility of adverse interactions between CAM and conventional medicines should be considered.
PP12.4	People who use CAM should be advised not to cease their insulin therapy because of the consequent high risk of diabetic ketoacidosis.
CAM, complementary and alternative medicine	

13 Maternal pregnancy and fetal outcomes

Type 1 diabetes per se is not a contraindication to pregnancy, and most women give birth to a healthy child, particularly if appropriate preconception and antenatal management is followed. However, elevated blood glucose levels are toxic to the developing fetus. There is a positive relationship between high levels of glycated haemoglobin (HbA_{1c}) early in pregnancy in women with type 1 diabetes and the risk of congenital malformations; rates may be many times those occurring in nondiabetic pregnancies (Ylinen et al 1984). Congenital malformations that are associated with type 1 diabetes include major anomalies such as cardiac and neural tube defects, and malformations of the renal and urinary tract, gastrointestinal and skeletal systems (Miodovnik et al 1988). There is also an association between poor glycaemic control early in pregnancy and miscarriage and perinatal mortality. In addition, adverse maternal outcomes, such as severe hypoglycaemia, are not uncommon (Robertson et al 2009a), and are increased in the first trimester compared with pre-pregnancy (Nielsen et al 2009). Pregnancy also accelerates ketosis and therefore there is a predisposition to ketoacidosis.

A prioritised, limited number of pregnancy related questions are addressed by these guidelines. For further information, we refer the reader to the Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy (McElduff et al 2005).

13.1 Effectiveness of preconception care

Question 13.1

What is the effectiveness of preconception care in women with type 1 diabetes on improving maternal and fetal outcomes?

The detailed systematic review of this question is in Chapter 13 of the accompanying technical report, and the evidence matrix is in Section C13 of Appendix C

Preconception care typically includes a strong focus on intensive blood glucose control, but also includes diabetes complications screening, medication review, folate supplementation, and discussion of smoking and alcohol intake.

This question considered the effectiveness of preconception care on improving pregnancy outcomes for the fetus and the mother. The systematic literature search identified one systematic review and 10 cohort studies examining the effectiveness of preconception care in women with type 1 diabetes. The systematic review (Ray et al 2001) included 16 cohort studies (8 prospective and 8 retrospective). Most of the studies, including those in the systematic review, were of a low level of evidence. The nature of the question does not lend itself to a randomised controlled trial (RCT) study design, and no RCTs were identified. Most of the studies were of fair quality and some of poor quality. Limitations in some studies included an unclear description of the preconception care intervention or the number who received preconception care, largely due to the studies being retrospective. One study included a mixed population, with participants who were recruited during either preconception or first trimester.

In the systematic review by Ray et al (2001) specific elements considered to be part of preconception counselling included screening for retinopathy and renal disease,

contraceptive advice, delay of conception until glucose control was optimised, target glucose levels, quantity and route of insulin administration, dietary advice and folic acid. They reported a significantly lower rate of major congenital anomalies among preconception care recipients compared with nonrecipients. Among 2561 offspring (14 studies), the pooled rate of major anomalies was 2.1% in recipients compared with 6.5% in nonrecipients (relative risk [RR] 0.36, 95% confidence interval [CI]: 0.22 to 0.59). In nine studies (2104 offspring) the risk for major and minor anomalies combined was also lower among women who received preconception care (RR 0.32, 95%CI: 0.17 to 0.59). In seven studies, early first trimester HbA_{1c} values were lower in the preconception care group (pooled mean difference: 2.3%, 95%CI: 2.1 to 2.4), but there was heterogeneity for this pooled estimate ($p < 0.20$).

Of the 10 additional cohort studies identified, results were mixed across various outcomes. Most of the studies found a reduced risk of an adverse fetal outcome with preconception care: five studies reported a reduced rate of perinatal mortality (McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010) and six studies found fewer congenital malformations (Goldman et al 1986; McElvy et al 2000; Boulot et al 2003; Temple et al 2006; Pearson et al 2007; Tripathi et al 2010). There was no significant effect of preconception care on maternal outcomes, including the rate of hypoglycaemia (Goldman et al 1986), the risk of severe hypoglycaemia (Temple et al 2006; Heller et al 2010), or the risk of pre-eclampsia (McElvy et al 2000; Temple et al 2006).

The evidence demonstrates that preconception care reduces the risk of congenital malformations and perinatal mortality among women with type 1 diabetes. Preconception care also appears to be effective at reducing HbA_{1c} levels at or around the time of conception. Many of the studies, including the systematic review of 16 cohort studies, only examined congenital malformations and perinatal mortality, and did not consider other maternal and fetal outcomes (e.g. birth weight, macrosomia, pre-eclampsia or the risk of severe hypoglycaemia).

Evidence statement	
Q13.1	Level III evidence shows that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA _{1c} levels in women with type 1 diabetes.
Recommendation	
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).
Practice points	
PP13.1.1	Counselling on contraception, pregnancy planning and preconception care should start during adolescence in females with type 1 diabetes.
PP13.1.2	At the time of planning pregnancy, females with type 1 diabetes should be referred to a multidisciplinary diabetes care team with expertise in preconception care. The team should consist of health professionals with an interest and experience in managing diabetes in pregnancy, including an obstetrician, an endocrinologist (or a physician experienced in diabetes care during pregnancy), a diabetes educator and a dietitian.
PP13.1.3	Intensive glycaemic management to optimise and maintain the HbA _{1c} level in a safe manner is an essential component of preconception care. This may take some 3 to 6 months to achieve.
PP13.1.4	There is an increased risk of neural tube defects in pregnancies in type 1 diabetes, so high-dose folic acid (5mg daily) supplementation should be started at least one month before conception, and continued for at least 3 months into the pregnancy.
PP13.1.5	Screening for diabetes complications specifically for diabetic retinopathy and nephropathy, should occur during preconception care.
PP13.1.6	Preconception care should include a strong focus on intensive blood glucose control prior to conception, complications screening, folate supplementation, discussion of smoking and alcohol intake, and review of medications. Statins, ACEI and ARBs are contraindicated in pregnancy.
PP13.1.7	Glycaemic control should be optimised before starting assisted reproduction procedures.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HbA _{1c} , glycated haemoglobin	

13.2 Effectiveness of blood glucose control

Question 13.2

What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?

The detailed systematic review of this question is in Chapter 13 of the accompanying technical report, and the evidence matrix is in Section C13 of Appendix C

The most readily demonstrable benefit of intensive blood glucose control in pregnancies of women with type 1 diabetes occurs in preconception care (as described in Section 13.1). Question 13.2 considered whether blood glucose control *during* pregnancy could lead to improved pregnancy outcomes for the mother with type 1 diabetes and her fetus.

The systematic review found only one Level I study that met the inclusion criteria (Middleton et al 2010). This Cochrane review was of high quality. The authors used a rigorous and detailed search methodology that was updated monthly until May 2010. The review included three RCTs, two from the United States and one from Saudi Arabia, with a total of 223 women and babies. There was a high risk of bias for all three trials due to unclear allocation concealment methods and a lack of blinded outcome assessment, as well as a high risk of selective outcome reporting bias.

The Cochrane review divided the studies into different categories of targeted glycaemic control: ‘very tight’ (fasting blood glucose [FBG] level <5 mmol/L), ‘tight’ (<6 mmol/L), ‘moderate’ (<7 mmol/L) and ‘loose’ (<9 mmol/L). In pooled analysis of two of the trials (Demarini et al 1994; Sacks et al 2006) glycaemic control was significantly better in the very tight target group compared with a tight–moderate group in the first (mean difference [MD] –1.23 mmol/L, 95%CI: –2.19 to –0.27) and second (MD –0.99 mmol/L, 95%CI: –1.64 to –0.34), but not the third trimesters (MD –0.66 mmol/L, 95%CI: –1.60 to 0.28). Few differences in outcome for mother or fetus were seen across these two trials. The single trial involving 60 women and babies that compared tight (\leq 5.6 mmol/L), moderate (5.0–6.7 mmol/L) and loose (6.7–8.9 mmol/L) glycaemic control targets found few differences between tight and moderate groups (Farrag 1987). In the loose control group, there were significantly more pre-eclampsia events, caesarean sections, neonates with respiratory distress syndrome, and cases of birth weight greater than the 90th percentile.

Thus, based on limited evidence, there were few differences in outcomes between very tight and tight–moderate glycaemic control targets in pregnant women with type 1 diabetes, including the actual level of glycaemic control achieved. There was some evidence of harm (increased pre-eclampsia, caesareans, respiratory distress syndrome and birth weight greater than 90th percentile) for loose glycaemic control (FBG above 6.7 mmol/L). The potential benefits of setting very tight glycaemic targets need to be balanced against the risk of severe hypoglycaemia occurring in the pregnant woman.

The systematic review did not include data from the Diabetes Control and Complications Trial (DCCT) because it was not designed to examine the effect of glycaemic control on pregnancy outcomes. It is noteworthy, however, that maternal and fetal outcomes were better in those randomised to the intensive treatment arm of the DCCT and who received preconception care.

It is important to note that in gestational diabetes mellitus, regimens targeting very tight blood glucose control before and after meals in the third trimester reduced adverse maternal and fetal outcomes (Crowther et al 2005). In type 1 diabetes, however, the potential benefit of setting very tight glycaemic targets needs to be balanced against the risk of severe hypoglycaemia occurring in the pregnant woman.

Evidence statement	
Q13.2	During pregnancy in women with type 1 diabetes, there is some evidence of harm for fasting blood glucose targeted at 6.7–8.9 mmol/L, compared to below 6.7 mmol/L.
Recommendation	
	There was insufficient evidence to make a recommendation.
Practice points	
PP13.2.1	Intensive management to achieve and then maintain optimal glycaemic control should occur throughout pregnancy and ideally commence preconception.
PP13.2.2	Care should be provided by a multidisciplinary team experienced in the management of diabetes in pregnancy.
PP13.2.3	The potential benefits of tight glycaemic control should be balanced against the risk of severe hypoglycaemia during pregnancy.
PP13.2.4	For type 1 diabetes in pregnancy a target HbA1c of <6.0% is desirable but unless this can be achieved safely, a conservative target of <7.0% is recommended.

13.3 Effectiveness of insulin pumps and CGMS during pregnancy

This section was not systematically reviewed as such there are no recommendations or practice points made. Further, the EAG considered that it is beyond the scope of this document to address every aspect of clinical care in pregnancy in type 1 diabetes. Pregnancy related items not addressed in this current guideline include schedules of care and monitoring of the progressive wellbeing of mother and fetus, management of delivery and its timing and postpartum management. The narrative contains information from the Australasian Diabetes in Pregnancy Society (ADIPS) consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy (McElduff et al 2005).

13.3.1 Effect of CSII in pregnancy on achieving blood glucose targets and improving maternal and fetal outcomes?

Currently, there is no high-level evidence to address whether insulin delivery by continuous subcutaneous insulin infusion (CSII) therapy has any different effect on outcomes for the pregnant woman or fetus from the use of multiple daily injections (MDI) of insulin, in either preconception care or during pregnancy. In pregnancy RCTs with a subsequent meta-analysis in a Cochrane systematic review have not shown any difference in glycaemic control or other outcomes between MDI and CSII strategies (Farrar et al 2007).

13.3.2 Effect of CGMS, real-time blood glucose monitoring and sensor-augmented CSII therapy in pregnancy on achieving blood glucose targets and improving maternal and fetal outcomes?

Use of continuous glucose monitoring systems (CGMS) in type 1 diabetes pregnancy may aid clinical decision making in pregnancy and is well tolerated (McLachlan et al 2007). However, there is no Level I or II evidence assessing whether CGMS or real-time blood glucose monitoring may improve pregnancy outcomes in type 1 diabetes. As described in Chapter 7 (question 7.2), the combination of CSII and continuous real-time monitoring of blood glucose (as sensor-augmented CSII therapy) was shown in one recent RCT to improve HbA_{1c} levels in type 1 diabetes outside of pregnancy (Bergenstal et al 2010). Such studies have not yet been undertaken in type 1 diabetes and pregnancy. In a RCT of 71 women with type 1 and type 2 diabetes, the use of CGMS as an educational and retrospective decision making tool resulted in lower HbA_{1c} levels ($5.8 \pm 0.6\%$) at 32-36 weeks compared with standard care ($6.4 \pm 0.7\%$, $p=0.007$). Birth weight centile was lower ($p=0.02$) and there was less macrosomia ($p=0.05$). Although the authors did not perform a sub analysis on subjects with type 1 diabetes, there is no reason to believe that CGMS would be less effective in pregnant women with type 1 diabetes (Murphy et al 2008).

13.4 Diabetes complications monitoring during pregnancy

During pregnancy in type 1 diabetes, microvascular complications – specifically retinopathy (Vestgaard et al 2010) and nephropathy – may worsen in an accelerated manner (Yogev et al 2010), especially in the overweight. The cause for this deterioration may be related to rapidly improved glycaemic control leading into and during pregnancy, the haemodynamic stress of pregnancy, and effects of various placentally derived and other hormones and growth factors during pregnancy (Kaaja 2009). Women with vision-threatening retinopathy should ideally receive photocoagulation therapy before conception. Patients with microalbuminuria before pregnancy are at increased risk of developing pre-eclampsia (Ekbom et al 2001). If renal function is significantly impaired with overt diabetic nephropathy (serum creatinine >0.2 mmol/L) (Biesenbach et al 1992), there is an increased risk of progression to dialysis during pregnancy. Therefore, chronic kidney disease stages 3B or higher should be considered a contraindication to pregnancy (McElduff et al 2005). The

presence of autonomic neuropathy resulting in gastroparesis, orthostatic hypotension or hypoglycaemic unawareness may severely complicate the management of pregnancy in type 1 diabetes; however, these conditions are not generally viewed as contraindications to pregnancy. Evidence of macrovascular disease should be sought through detailed history and examination, and investigated if suspected. Pre-existing heart disease, including coronary heart disease, requires cardiological review before pregnancy, and significant coronary artery stenosis should be treated before conception (McElduff et al 2005).

There are no Level I or II studies that address the nature and timing of diabetes complications monitoring during pregnancy in type 1 diabetes. For complications, screening recommendations from professional bodies such as the ADIPS (McElduff et al 2005) indicate that, in women without a known history of microvascular complications, screening at least once during the pregnancy should occur for the diabetes microvascular complications of retinopathy and nephropathy, using standard methods. Such screening should preferably be undertaken in the first trimester, especially if complications screening has not recently been done. Those with known diabetic retinopathy or nephropathy before pregnancy are at high risk. In such cases, monitoring during pregnancy and related management should be individualised by the health care professional multidisciplinary unit supporting the pregnancy. For example, monitoring of retinopathy and nephropathy (including assessment of albuminuria and determination of estimated glomerular filtration rate) could be undertaken each trimester. It is recommended, as a guide, that formal eye review for diabetic retinopathy should be undertaken at least 3-monthly if baseline retinopathy is present, if there is a rapid improvement in glycaemic control, or if there has been a long duration of pre-existing diabetes (McElduff et al 2005). More frequent monitoring of complications status may be indicated for pregnant women who have required recent photocoagulation therapy, have systemic hypertension or have overt diabetic retinopathy (Kaaja 2009). Recent data from women with diabetic nephropathy before pregnancy indicate that strict control of blood pressure and blood glucose can lead to improved pregnancy outcomes, compared with historic controls (Nielsen et al 2009).

13.4.1 Summary

Screening for diabetes complications, specifically diabetic retinopathy and nephropathy, should not only occur as part of preconception care, but also during pregnancy, preferably in the first trimester. Vision-threatening diabetic retinopathy should be managed before conception, since retinopathy can worsen during pregnancy. The presence of significant chronic kidney disease is a relative contraindication to pregnancy in type 1 diabetes; the risks of pregnancy in this setting should be discussed before conception. In women who have diabetic retinopathy or nephropathy before pregnancy, processes for monitoring these complications throughout pregnancy should be individualised, as scheduled by the multidisciplinary high-risk pregnancy diabetes health professional care team.

Periodic use of CGMS or real-time blood glucose monitoring during pregnancy may aid modification of intensive insulin therapy regimens during pregnancy. Intensive diabetes management during pregnancy includes multidisciplinary specialist care and may involve the use of CSII. Insulin requirements fall rapidly during labour and in the puerperium. At this time, close monitoring and adjustment of insulin therapy is indicated.

Level 3 neonatal nursery facilities may be required and should be anticipated when birth occurs before 36 weeks, or if there has been poor glycaemic control.

As there is an increased risk of psychological disorders among young women with diabetes (see chapter 4), the practitioner should maintain a high level of vigilance for depression, anxiety, and eating disorders.

14 Contraception

14.1 Introduction

Reliable methods of contraception are needed in women with type 1 diabetes, not least because planned pregnancy is necessary to optimise fetal and maternal outcomes in pregnancy. The options in contraception are broadly divided into hormonal and nonhormonal methods. Both efficacy and potential adverse effects, including those related to diabetes, need to be assessed to examine effectiveness. This chapter examines the effectiveness of hormonal versus non-hormonal contraception on type 1 diabetes.

Question 14.1

What is the effectiveness of hormonal versus non-hormonal contraception in type 1 diabetes?

The detailed systematic review of this question is in Chapter 14 of the accompanying technical report, and the evidence matrix is in Section C14 of Appendix C

In a review of the published literature, one systematic review (Visser et al 2006) met the inclusion criteria, and had been updated in 2009. This systematic review aimed to capture all published data from randomised controlled trials (RCTs) and quasi-randomised trials that compared differences between progestogen-only contraceptive methods, combined oestrogen/progesterone contraceptives, and nonhormonal contraceptives in women with diabetes. The comparisons were in terms of effectiveness in preventing pregnancy, effects on carbohydrate and lipid metabolism, and long-term outcomes such as vascular complications.

The four RCTs in the systematic review differed in terms of the contraceptives studied, participant characteristics and methodological quality (Radberg et al 1982; Skouby et al 1986; Rogovskaya et al 2005; Grigoryan et al 2006); thus, data could not be combined in a meta-analysis. The trial results were examined on an individual quantitative basis and narrative summaries were reported. The hormonal contraceptives included differing doses (low and higher dose) of oestrogen, androgenic and nonandrogenic progestogens (either alone or with oestrogen), and intrauterine devices (IUDs) that contain copper or release levonorgestrel. Outcomes of interest included metabolic outcomes (e.g. glycaemia, insulin requirements, and lipid profiles), as well as body weight and effects on blood pressure.

There were no unintended pregnancies during any of the included trials. Since pregnancy is a rare event in contraceptive users, the sample size and duration of the included trials were too small and too short, respectively, to detect differences among the various contraceptives. From large trials conducted among contraceptive users in the general population, it is known that, with proper use of contraceptives (as occurred in the included trials), combined oral and progesterone-only contraceptives give a 0.3% chance of an unintended pregnancy within the first year. This chance is 0.6% for copper IUDs and 0.1% for progestogen-releasing IUDs (WHO 2004). It is expected that the chance of an unintended pregnancy is similar for women with diabetes, relative to women without diabetes, when such contraception is used.

In relation to metabolic outcomes, the studies did not show benefit or adverse effect on glycaemia. The three studies that reported lipid levels, including cholesterol subsets, gave

conflicting results, although all lipid levels were within normal range before and after contraceptive use. The studies that examined blood pressure (Radberg et al 1982; Skouby et al 1986) found no change in this parameter across the 6-month study duration, nor did body weight change (Skouby et al 1986). The RCTs had some limitations, including poor reporting of study methods and poor methodological quality. Three of the four included studies did not describe the method of generating the allocation sequence, the method of concealing the treatment allocation sequence, or the use of blinding. At 12 months' maximal duration, none of the studies were of adequate duration to assess for any direct effect on diabetes end-organ complications.

14.2 Summary

Overall, the data did not provide sufficient evidence to assess whether progesterone-only or combined oral contraceptives differ from nonhormonal contraceptives in their effects on diabetes control, lipid metabolism and long-term diabetes-related complications. Unintended pregnancies were not observed during any of the studies. Three of the four studies were of limited methodological quality and described surrogate outcomes.

Evidence statements	
Q14.1	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on glycaemic control. The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on lipid metabolism.
Recommendation	
	There was insufficient evidence to make a recommendation.
Practice points	
PP14.1	The relative risk of unplanned pregnancy should be considered against the potential cardiovascular risk associated with systemic hormonal contraceptives.
PP14.2	Non-hormonal contraceptive methods (e.g. IUD methods, condoms) can be effective and are generally well tolerated.
PP14.3	Contraceptive preferences will often differ across women of reproductive age; for example, between an adolescent with type 1 diabetes and a 40–45-year-old woman.
PP14.4	In a stable long-term relationship, male contraception through vasectomy is an effective non-hormonal permanent contraceptive method.
ACEI, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; IUD, intrauterine device; RCT, randomised controlled trial	

15 Transition of care from paediatric to adult health services

This chapter was not systematically reviewed; it is based on contemporary evidence based guidelines from the International Society for Paediatric and Adolescent Diabetes (Court et al 2009). The chapter also draws extensively on the *Best practice guidelines for health professionals* for the effective transition of young people with diabetes from paediatric to adult care (Lang 2008). There are no recommendations or practice points made in this chapter; the reader should refer to these documents for further information.

15.1 Essential elements in transitional care models from adolescence to adulthood

The most useful definition for transition comes from the American Society for Adolescent Medicine, where it is described as ‘the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-orientated health care systems’ (Blum et al 1993). Key elements required for effective transitional care, discussed below, include:

- flexible timing of transfer
- flexibility in provision of health services
- a ‘transition case manager’ for each person
- a preparation period
- a choice of adult provider
- a coordinated transfer
- joint consultations
- accessible medical documentation
- maintaining contact after transfer
- psychosocial support

Flexible timing of transfer

There is no ‘set’ or ‘right’ time for transition. Each person should be viewed as an individual and consideration should be given to the person’s developmental and health status, and to contemporary events in their life. However, establishing a target transfer age is useful for planning by the care team, and for preparing the young person for an anticipated change. Young people generally should not be transferred to a new service or clinic at a time that coincides with major life changes or when in ‘crisis’.

Flexibility in provision of health services

Health services need to be flexible and designed to suit the needs of young people; examples include evening clinics and young adult clinics.

A ‘transition case manager’ for each person

Each young person should be assigned a transition case manager from within the multidisciplinary diabetes care team. The role of the manager includes monitoring and

documenting the young person's progress through the transition process. The manager can either intervene where necessary, or arrange appropriate interventions from other members of the care team; for example, if the young person fails to attend a clinic appointment or has evidence of poor glycaemic control. The transition case manager becomes the primary contact for the young person.

A preparation period

A preparation period is necessary to help young people develop the necessary knowledge and skills to enable them to cope with the responsibilities of taking charge of their own diabetes health care.

A choice of adult provider

Where possible, young people should be given a choice of adult care provider, and should be reassured that it may take more than one visit to a doctor or service to find someone with whom they feel comfortable. Options should include care in the private sector.

A coordinated transfer

Young people should be given an anticipated transfer date or an age of transfer to adult services. Preferably, before transfer, there should be an opportunity for at least one visit with the adult service or clinic (Kipps et al 2002), which may be a joint visit if practicable.

Accessible medical documentation

A comprehensive medical and psychological history, along with a treatment summary, should accompany the young person when they are transferred to an adult service. Documentation of education and skills acquisition should also be included. The young person's consent needs to be obtained for the release of this information (Viner 1999).

Maintaining contact after transfer

The transition case manager should maintain contact with the young person after transfer, to ensure that their needs are met by the adult diabetes service to which they are transferred. Young people need to be supported in finding an adult diabetes service that they feel comfortable with. Contact should be maintained until the young person has successfully engaged with an adult diabetes service.

Psychosocial support

During the transition process, the psychosocial needs of the young person must be proactively anticipated and managed (Royal College of Physicians of Edinburgh Transition Steering Group 2008). Additional psychological support is likely to be required as the time of transfer to adult care approaches. The diabetes care team must also be aware of the prevalence of depression in young people with diabetes. Behavioural problems and declining school performance can be specific markers of underlying psychological distress in adolescence (Department of Health Western Australia 2009).

15.2 Adult diabetes health service

Adult health care differs significantly from paediatric care in relation to the type and level of support, decision-making, consent processes and family involvement. These factors may contribute to the decrease in attendance by young people after transfer to the adult care system. Many young people are lost to specialist diabetes care after transfer to an adult service (Nakhla et al 2009). The rate of young people lost to adult care varies from 11% to 50% (Frank 1996; Pacaud et al 2005; Perry et al 2010). Factors predicting failure of transition

to adult care include lack of regular clinic attendance by adolescents and poor glycaemic control (Frank 1996; Jacobsen et al 1997; Goyder et al 1999).

Health professionals tend to focus on future benefit from current treatment, whereas young people tend to be focused on the 'here and now'. Ongoing review of diabetes care priorities with the young person may help them to take ownership of, and responsibility for, their health care (Royal College of Physicians of Edinburgh Transition Steering Group 2008).

Elements of adult diabetes care that contribute to successful transition include providing adequate psychological support, tailoring treatment and maintaining confidentiality. A survey of young people with diabetes investigated what young people want from an adult diabetes service (Dovey-Pearce et al 2005). Given the high proportion of young people with diabetes who 'drop out' of conventional adult care, adult services may consider adopting some, if not all, of the following practices, to meet the specific needs of young people:

- ensuring that the young person sees the same staff at each consultation or clinic visit
- providing definite appointment times
- providing capacity for 'drop in' visits
- holding clinics and consultations out of working hours (including weekends)
- providing specific clinics for young adults
- encouraging questions during clinics and consultations
- taking an interest in the patient as a person
- providing information relevant to the young person
- providing resources (e.g. list of appropriate websites, booklets, videos)
- providing regular updates (e.g. through a newsletter)
- encouraging telephone or email contact with staff
- sending SMS reminders for appointments
- implementing a patient feedback process.

An Australian study demonstrated that a post-transition program of care, which incorporated many of the above features, was associated with low 'drop-out' rates at two years (Holmes-Walker et al 2007).

15.3 The role of the general practitioner

The general practitioner (GP) has an important role as a partner in the management of all young people with diabetes, and should be the primary point of contact for the young person and their family for day-to-day health issues. The diabetes care team has a responsibility to keep the GP informed of the young person's progress and current treatment.

The GP has a critical role in ensuring continuity of care, particularly during transition. In the absence of a suitable adult diabetes service, the GP may become responsible for the young person's diabetes management after transfer from paediatric care. It is essential that the GP screens for diabetes complications, and immediately refers the young person to a diabetes specialty service if any of the following apply:

- there are any abnormal findings on the annual diabetes complication screen
- the HbA1c is above 9% on two or more occasions in one year
- there is continued and significant weight loss
- the body mass index is below 18 kg/m² or above 25 kg/m²
- the young person is not, or experiencing difficulty with, adhering to the treatment regimen
- the young person is pregnant or is considering becoming pregnant
- the young person has been admitted to hospital for a diabetes-related condition (e.g. ketoacidosis or severe hypoglycaemia)
- there is a diagnosis of one or more coexisting diseases
- there are any mental health issues.

15.4 Summary

Transition must never be rushed. Rather, it needs to occur in a purposeful, structured, coordinated manner beginning in early adolescence. It is appropriate to give greater attention to the cohort of adolescents who are not attending clinic regularly and who have poor glycaemic control, as this may improve transition outcomes. Evidence suggests that these factors are predictors of failure in transition to adult care (Frank 1996; Jacobsen et al 1997; Goyder et al 1999).

During the transition process, the focus should progressively switch from the parent as the caregiver to acknowledging the growing autonomy of the young person. Therefore, the transition program must be aimed at engaging the young person in their care and ensuring they have the appropriate knowledge and skills to make informed health decisions (Viner 2001). As well as dealing with the medical issues of the young person, education needs to include (McDonagh and Viner 2006):

- skills training, including diabetes self-management, self-advocacy, and the ability to independently negotiate services and to actively participate in a medical consultation
- education about general adolescent health issues, such as drug taking, alcohol use, and mental and sexual health issues
- educational and vocational issues, particularly career, work experience and disclosure

Successful transition requires an interested and capable adult diabetes service (public or private) and a willingness by the adult health professionals to participate in the transition process. Both paediatric and adult teams need to be responsive to the needs of young people if transition is to be successful. The manner in which the young person is prepared for transition to the adult health-care system is crucial to their continued wellbeing and adherence to ongoing health support and treatment. Young people with diabetes should be informed of the important role their GP has in ensuring continuity of health care generally and of diabetes care specifically.

16 Hypoglycaemia

Hypoglycaemia occurs when the blood glucose level falls below normal and the person experiences related symptoms that resolve after the blood glucose returns to normal (Cryer et al 2009). Hypoglycaemia in type 1 diabetes results from a clinically significant mismatch between insulin administered and insulin required for the person's lifestyle requirements (Cryer et al 2009). There is no consistent agreed upon single numerical definition of hypoglycaemia, although a blood glucose level at or less than 3.9 mmol/L on laboratory testing is used as a level that typically would signify a hypoglycaemia range level (2005).

Hypoglycaemia is considered mild when people are able to treat themselves. The common definition used for severe hypoglycaemia is that the hypoglycaemia episode requires assistance from a third party to treat the hypoglycaemia and it is usually associated with some acute impairment of cognitive functioning (DCCT Research Group 1993). Grade 2 (also known as moderate hypoglycaemia) is where unconsciousness has not occurred and yet assistance from a third party is required and grade 3 is hypoglycaemia resulting in unconsciousness or seizure. For the purposes of this Guideline and the related systematic reviews, both grade 2 and 3 hypoglycaemia were accepted as 'severe hypoglycaemia', as per the DCCT Research Group definition. Severe hypoglycaemia may be life threatening; for example, by causing injury or precipitating cardiac events (Cryer 2010). It is a major endpoint to target in the professional care of type 1 diabetes (DCCT Research Group 1993). Hypoglycaemia of all forms is generally feared by people with diabetes and their immediate carers and family (Anderbro et al 2010; Barnard et al 2010). Fear of hypoglycaemia and its consequences, including nocturnal episodes, is often the greatest barrier to optimal glycaemic control (Pearson 2008).

Mild hypoglycaemia remains a regular occurrence for most people with type 1 diabetes; for example, in the intensive management group of the DCCT, mild hypoglycaemia occurred about twice weekly (DCCT Research Group 1993), and may adversely affect quality of life. In contrast, severe hypoglycaemia occurs on average once every three or more years in type 1 diabetes (Jones and Davis 2003). There is marked individual variation in the rate of severe hypoglycaemia, with some people never experiencing it and others experiencing it multiple times a year, despite intensive diabetes management in multidisciplinary diabetes health-care units (DCCT Research Group 1997). Nocturnal hypoglycaemia accounts for close to half of the episodes of severe hypoglycaemia (Allen and Frier 2003).

Risk factors for severe hypoglycaemia and acute effects are discussed in Section 16.2; cognitive effects that can occur due to severe hypoglycaemia in Section 16.3; and efficacy and safety of treatments for hypoglycaemia in Section 16.4.

16.1 Predictive factors for severe hypoglycaemia

Question 16.1

- i) What are the predictive factors for severe hypoglycaemia?
- ii) What is the effect of intensive diabetes management on the incidence of severe hypoglycaemia?

The detailed systematic review of this question is in Chapter 16 of the accompanying technical report, and the evidence matrix is in Section C16 of Appendix C

Severe hypoglycaemia is about 10 times more common in people with type 1 diabetes than in those with type 2 diabetes (DCCT Research Group 1991; UKPDS Group 1998b; DCCT Research Group 2009). In severe hypoglycaemia, the person with diabetes is unable to treat himself or herself, and the hypoglycaemia may lead to accident and precipitate medical emergencies. Methods to identify risk factors for severe hypoglycaemia in a person with type 1 diabetes, and to minimise the occurrence of severe hypoglycaemia, are therefore of high priority. Severe hypoglycaemia may be more common in settings where attempts to reduce risk of long-term end-organ complications of diabetes are instituted.

The risk factors for severe hypoglycaemia include those that are inherent in the individual with diabetes and those that are a consequence of treatment of diabetes. This question was divided into two parts to examine the evidence for these factors separately.

16.1.1 Predictors of severe hypoglycaemia

In addressing question 16.1 (i), the systematic review was subdivided into children/adolescents and adults, because predictors of severe hypoglycaemia may differ across the life span.

Children and adolescents

The systematic review identified Level II (prospective cohort) studies, which ranged from 61 (Gonder-Frederick et al 2008) to more than 7605 person years of follow-up (Bulsara et al 2007). In addition, three cross-sectional studies were identified, each of which surveyed more than 2000 young people with type 1 diabetes (Mortensen and Hougaard 1997; Danne et al 2001). In adults, the highest level evidence came from a randomised control trial (RCT) – the DCCT (DCCT Research Group 1993). Two analyses of this population were included (DCCT Research Group 1991; DCCT Research Group 1997), with a follow-up time of more than 9000 person years. Six adult cross-sectional studies were also identified (Chaturvedi et al 1995; Stephenson et al 1996; Buyken et al 1998; Salti et al 2004; Hirai et al 2007; Pedersen-Bjergaard et al 2008). Overall, studies were mostly of good or fair quality.

Study outcomes are summarised and tabulated in the technical document. Age was an independent risk factor for severe hypoglycaemia in children and adolescents; severe hypoglycaemia was more common in children younger than 6 years compared with older children (Davis et al 1998; Bulsara et al 2004; Bulsara et al 2007). Increasing duration of diabetes, especially after more than 9 years, was positively associated with severe hypoglycaemia (Bulsara et al 2004; Bulsara et al 2007) and the risk increased progressively with each 5 years of diabetes in the paediatric age group (Rewers et al 2002).

Lower glycated haemoglobin (HbA_{1c}) level was also consistently a risk factor for severe hypoglycaemia across seven studies reported, including in the DCCT (DCCT Research Group 1994). In one study, for each 2% reduction in HbA_{1c} level, the severe hypoglycaemia risk increased 1.5 fold (95% confidence interval [CI]: 1.2 to 2.0) (Allen et al 2001), reflecting a similar finding in one Australian study across the HbA_{1c} range of 7–9% (Davis et al 1998). Other factors associated with increased risk of severe hypoglycaemia were the conditions of reduced hypoglycaemia awareness (i.e. reduced ability to detect early warning symptoms of hypoglycaemia) (Gonder-Frederick et al 2008) and psychiatric illness (Rewers et al 2002), although these conditions were not well examined, due to exclusion criteria in many studies. For teenagers, being male was implicated as a risk factor in one study (Bulsara et al 2004), but not another (Rewers et al 2002). Social disadvantage (Bulsara et al 2004), higher insulin dose and serum angiotensin converting enzyme (ACE) level, were also risk factors. In the DCCT, adolescents in both the conventionally and intensively managed groups had a higher

rate of severe hypoglycaemia compared with adults in the trial (DCCT Research Group 1994). Across all the risk factors in children and adolescents, significant odds ratios (ORs) for severe hypoglycaemia were generally in the range 1.5–3.0, with the most robust associations being found for longer diabetes duration, age less than 6 years and lower HbA_{1c} level.

Adults

Risk factors for severe hypoglycaemia included increasing diabetes duration (DCCT Research Group 1997), lower HbA_{1c} level (DCCT Research Group 1997) and male sex (DCCT Research Group 1997), in keeping with evidence from studies in young people. The original DCCT report indicated a continuous, apparently exponential, increase in severe hypoglycaemia risk with lower HbA_{1c} levels (DCCT Research Group 1993). A more recent publication using the DCCT cohort reported a hazard ratio of 0.93 for a higher HbA_{1c} and severe hypoglycaemia ($p < 0.001$); the study also suggested that mean blood glucose and standard deviation add to the risk, independently of HbA_{1c} level (Kilpatrick et al 2007). A previous history of severe hypoglycaemia was also an independent risk factor for severe hypoglycaemia (Kilpatrick et al 2007). The ORs for severe hypoglycaemia were generally in the range 1.5–3.0 with the higher ratios being observed in those with a longer diabetes duration, lower HbA_{1c} level or previous severe hypoglycaemia. In addition, in various studies, risk factors for severe hypoglycaemia were found to include hypoglycaemia unawareness (Pedersen-Bjergaard et al 2008), presence of autonomic neuropathy (Hirai et al 2007), current smoking (Hirai et al 2007), angiotensin 2 receptor allele genotype, a higher serum ACE level (Pedersen-Bjergaard et al 2008) and prolonged fasting in those with type 1 diabetes who practise Ramadan (Salti et al 2004). Increasing age in adults was an independent risk factor for severe hypoglycaemia in one study (Pedersen-Bjergaard et al 2008) but not in another (Kilpatrick et al 2007).

16.1.2 The effect of intensive diabetes management on the incidence of severe hypoglycaemia

The systematic review identified two meta-analyses that examined the risk of adverse effects of intensified treatment in type 1 diabetes. Wang et al (1993b) was published before the DCCT, and was of fair quality. The meta-analysis by Egger et al (1997b) included the results of the DCCT and was of good quality. These two studies provided Level I evidence that intensified diabetes management significantly increased the risk of severe hypoglycaemia.

In the meta-analysis by Egger et al, which included a total of 2067 patients, the incidence of severe hypoglycaemia ranged from 0 to 66.6 (median 7.9) episodes per 100 person years among intensively treated patients, and from 0 to 33.3 (median 4.6) episodes among conventionally treated patients. The combined OR reported by Egger et al (1997b) was 2.99 ($p < 0.0001$) for intensively treated patients, with some evidence for heterogeneity across studies ($p = 0.06$). The DCCT trial reported a relative risk of 3.28 for severe hypoglycaemia in patients from the intensive treatment arm compared to the conventional group. The meta-analysis published before the DCCT results showed a trend towards an increase in severe hypoglycaemia with intensively treated patients; however, this was not statistically significant (Wang et al 1993b) – the estimated difference between arms being 9.1 (95%CI: – 1.4 to 19.6). These results were pooled from six small studies (with numbers ranging from 20 to 94 participants), with overall low incidence rates of severe hypoglycaemia.

The definition of severe hypoglycaemia varied somewhat in the studies included in this systematic review. Most studies followed the DCCT definition of severe hypoglycaemia, as hypoglycaemia requiring the assistance of a third party (DCCT Research Group 1993). Some defined severe hypoglycaemia more strictly as that resulting in seizure or coma or hospital

admission, or requiring parenteral therapy. Therefore, these latter studies may underestimate the prevalence of any severe hypoglycaemia that required third-party help but did not result in unconsciousness. In addition, the threshold at which children need assistance from a third party may differ from that of adults. Davis et al (1998) attempted to address this by including only episodes accompanied by obvious neuroglycopenia. In addition, the issue of recurrent severe hypoglycaemia was not always addressed in the included studies and was not included as an outcome for this report. People with a history of prior severe hypoglycaemia were often excluded from the studies addressing severe hypoglycaemia. In adults, severe hypoglycaemia tends to recur and 'cluster' in certain high-risk individuals (e.g. people with more than 10 years of type 1 diabetes, with past history of severe hypoglycaemia and reduced hypoglycaemia awareness), especially if chronic behavioural or psychological disorders exist that can reduce adherence to matching insulin doses to lifestyle needs and in monitoring blood glucose.

In clinical practice, the frequency of severe hypoglycaemia need not always increase with lower HbA1c levels. When implemented as part of continuous quality-assurance, a structured education and self-management programme in type 1 diabetes may lead to improvement in glycaemic control without increasing the risk of severe hypoglycaemia (Samann et al 2005). While these data are not derived from a randomised controlled trial, it does suggest that structured health care delivery in diabetes can help to minimise risk of severe hypoglycaemia during intensified glycaemic control. Through the health carer and person with diabetes identifying and discussing risk factors for severe hypoglycaemia, including potentially reversible risks, the occurrence of such episodes may be minimised.

Evidence statements	
Q16.1	Level I evidence from studies published before 1997 (including the DCCT) shows that intensive management is associated with a higher risk of severe hypoglycaemia. Level II evidence indicates that younger age, longer duration of diabetes and hypoglycaemia unawareness are associated with higher risk of severe hypoglycaemia.
Recommendation	
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).
Practice points	
PP16.1.1	Minimising severe hypoglycaemia is important, including as a component of intensive diabetes management.
PP16.1.2	Intensive diabetes management may increase the risk of severe hypoglycaemia; therefore, some people who have a high risk of severe hypoglycaemia may not be suitable for the usual tight HbA _{1c} targets.
PP16.1.3	Recognised risk factors that increase severe hypoglycaemia risk include alcohol abuse and recreational drug abuse; these should also be addressed in people with type 1 diabetes.
PP16.1.4	Specific management strategies should be implemented for people who have a high risk of severe hypoglycaemia, including those with a history of severe hypoglycaemia or a reduced ability to detect early warning symptoms of hypoglycaemia (i.e. hypoglycaemia unawareness). In cases of hypoglycaemia unawareness, strategies to reduce severe hypoglycaemia include more frequent SMBG, and ensuring that any blood glucose below a certain threshold (e.g. <4 mmol/L) is treated as hypoglycaemia, even in the absence of hypoglycaemic symptoms.
PP16.1.5	A medical practitioner should carefully assess whether a person with type 1 diabetes is fit to drive a motor vehicle, this is required, in particular, to help reduce the risk of motor vehicle crashes due to severe hypoglycaemia. The AustRoads <i>Assessing fitness to drive</i> booklet, should be used as a reference.
DCCT, Diabetes Control and Complications Trial; HbA _{1c} , glycated haemoglobin; SMBG, self-monitored blood glucose	

16.2 Acute effects of severe hypoglycaemia

Question 16.2

What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?

The detailed systematic review of this question is in Chapter 16 of the accompanying technical report, and the evidence matrix is in Section C16 of Appendix C

The systematic review identified 31 studies that met the inclusion criteria, three of which were prospective cohort studies in a naturalistic environment (Cox et al 1999; Cox et al 2005; Gonder-Frederick et al 2009). The other studies were labour-intensive laboratory studies with small participant numbers, where blood glucose levels were manipulated artificially by use of the insulin clamp method. All studies were undertaken in well-developed health-care systems, including one paediatric study in Australia (Davis et al 1996).

The prospective cohort studies collectively included 289 adults and 61 primary school aged children, and were of moderate risk of bias. Gonder-Frederick et al (2009) studied effects of hypoglycaemia and hyperglycaemia in school-aged children using a field procedure to test the hypothesis that naturally occurring episodes of hypoglycaemia and hyperglycaemia are associated with deterioration in cognitive function. Cox et al (1999) and (2005) examined adults with recent severe hypoglycaemia and current hyperglycaemia, respectively. The insulin clamp studies were predominately carried out in adults (total n=398), with only two being in children or adolescents (total n=48) (Gschwend et al 1995; Davis et al 1996). Studies were heterogeneous in terms of the methodologies used, including glycaemic thresholds at which cognitive function was assessed, the tests that were used to measure cognitive function, the timeframe in which assessment was undertaken, and the outcomes measured. In the cohort studies, both hypoglycaemia and hyperglycaemia were associated with impaired cognitive function (Cox et al 1999; Cox et al 2005; Gonder-Frederick et al 2009).

Children and adolescents

In children, during blood glucose extremes (defined as <3.0 mmol/L and >22.2 mmol/L), cognitive function was significantly affected, as demonstrated by longer time taken to complete mental mathematics and choice reaction time (Gonder-Frederick et al 2009). However, the studies each reported large differences between individuals in the degree of impairment occurring at different blood glucose levels (Cox et al 2005; Gonder-Frederick et al 2009). Demographic variables such as age and sex were not associated with individual differences; however, a relationship was demonstrated between higher HbA_{1c}, frequency of severe hypoglycaemia and greater cognitive impairment when blood glucose levels were high (Gonder-Frederick et al 2009). The reported limitations of these studies included the relatively small number of participants, most of whom were Caucasian (Gonder-Frederick et al 2009). In addition, the participants were studied over a relatively short period of time, yielding a limited number of extreme blood glucose readings (Gonder-Frederick et al 2009). The authors suggested that the results, especially those on acute hyperglycaemia, be considered preliminary and be interpreted with caution. Large individual differences were found, and numerous, unidentified variables were likely to have affected the impact of acute blood glucose extremes on cognitive function.

There was inconsistency in the results reported concerning the effects of acute hyperglycaemia on cognitive function in the two studies in children. Davis et al (1996) found a significant impact on performance intelligence quotient (IQ) in a group of 12 Australian children. Gschwend et al (1995) found no impact of acute hyperglycaemia on cognitive

performance, as measured by choice reaction time and the trail-making test, in a series of 10 teenagers (Gschwend et al 1995). This inconsistency may be due to the different methodologies used and the outcomes measured.

Adults

In adults, the negative impact on cognitive function when blood glucose level was less than 3.9 mmol/L was significantly greater when compared with the impact on those without a recent history of severe hypoglycaemia (Cox et al 1999). Among the insulin clamp studies, in those measuring the effect of hypoglycaemia on cognitive function, significant effects on both simple and more complex cognitive tasks were demonstrated compared to measures of cognitive function during euglycaemia. Decreases in psychomotor function, motor speed and reaction time, attention, verbal function, memory, visual spatial skills and auditory information processing were demonstrated in response to acute hypoglycaemia. Gonder-Fredrick et al (1994) found that glycaemic thresholds for, and recovery from, cognitive dysfunction varied greatly across individuals, ranging from glucose levels below 2.6 mmol/L to above 3.6 mmol/L (Gonder-Fredrick et al 1994). Hypoglycaemia unawareness was associated with more profound and longer lasting cognitive dysfunction (Gold et al 1995), and recent occurrence of nocturnal hypoglycaemia was associated with lower glycaemic thresholds for cognitive dysfunction (Fanelli et al 1998). Lower HbA_{1c} was also associated with lower glycaemic thresholds for cognitive dysfunction in one study (Ziegler et al 1992), but not in another (Maran et al 1995).

In the prospective cohort study, acute hyperglycaemia (defined as blood glucose level >15 mmol/L) had a significant impact on cognition, with slowing in all cognitive performance tests ($p < 0.02$) and an increased number of mental subtraction errors (Cox et al 2005). Abnormal test results in hyperglycaemia were observed in about 50% of adults studied and exploratory analyses undertaken to determine the basis of these individual differences demonstrated an association between cognitive impairment and greater exposure to blood glucose readings above 15 mmol/L and higher HbA_{1c} (Cox et al 2005). In contrast, there was no effect on cognitive function in two studies (Hoffman et al 1989; Draelos et al 1995). There were subtle trends towards poorer performance during hyperglycaemia in three studies by Holmes et al (1983; 1984; 1986).

Summary

Acute hypoglycaemia and acute hyperglycaemia may adversely affect cognitive function in children and adults. Data are less well established for acute hyperglycaemia, and there is much individual variation in threshold for effects and rate of recovery, only some of which may be explained by currently known variables.

In relation to the practical issue of diabetes, blood glucose and driving, consensus Australian guidelines indicate that: (i) the SMBG should be above 5 mmol/L prior to driving and, (ii) that while acute hyperglycaemia may affect some aspects of brain function, there is insufficient evidence to determine regular effects on driving performance and related crash risk; each person with diabetes should be counselled about management of their diabetes during days when they are unwell and should be advised not to drive if they are acutely unwell with metabolically unstable diabetes (Austroads 2006).

Evidence statements	
Q16.2	Level II evidence shows that acute hypoglycaemia causes a temporally related impairment in cognitive performance. Level III evidence shows that acute hyperglycaemia may cause cognitive impairment in children and adults. One Level II study shows that acute hyperglycaemia above 22 mmol/L in children is associated with a comparable impairment to acute hypoglycaemia (<3 mmol/L).
Recommendation	
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.
Practice points	
PP16.2.1	Adverse cognitive effects of acute severe hypoglycaemia and acute severe hyperglycaemia should be avoided during tasks requiring high level cognitive function, such as in school, college or university examinations; or in adolescents and adults during potentially dangerous activities involving occupational health, such as operating heavy machinery or during driving. In some cases, the risk or presence of acute severe changes in blood glucose to very low and possibly very high levels may lead to the need for exemption from or avoidance of the cognitively demanding or high-risk activity.
PP16.2.2	Mild hypoglycaemia and mild hyperglycaemia are common in type 1 diabetes; however, acute severe dysregulation of blood glucose to either extreme that may cause cognitive effects should be avoidable in most people with type 1 diabetes, if due self-care is taken.
PP16.2.3	The blood glucose level at which a person develops cognitive effects from severe hypoglycaemia can vary, related to the degree of chronic glycaemia control and avoidance of severe hypoglycaemia if an episode has occurred during recent weeks to months. In such cases, early warning symptoms of hypoglycaemia that may have been lacking in a person with type 1 diabetes may at least partially return.

16.3 Prevention of severe hypoglycaemia

Question 16.3

How can severe hypoglycaemia be prevented?

The detailed systematic review of this question is in Chapter 16 of the accompanying technical report, and the evidence matrix is in Section C16 of Appendix C

The objective of this question was to evaluate the evidence for any intervention primarily designed to prevent, reduce or avoid severe hypoglycaemia. The potential reduction of severe hypoglycaemia as a secondary outcome of specific interventions has been addressed by other systematic reviews in this series (see Chapter 7). The search strategy for this question focused on educational interventions.

Five studies met the criteria set for this question, with three of these being RCTs (Nordfeldt et al 2003; Nordfeldt et al 2005; Schachinger et al 2005) (Level II evidence). The other two studies were case series with outcomes before and after testing (Level IV evidence) and with significant potential for bias (Cox et al 2001; Broers et al 2005). Each study examined the effect of educational interventions on the reduction of severe hypoglycaemia. In all studies, severe hypoglycaemia was defined as an episode of hypoglycaemia requiring assistance. Participants' reports of severe hypoglycaemia were confirmed by blood glucose level diary in one study (Schachinger et al 2005). The two studies by Nordfeldt et al (2003; 2005) reported the results derived from the same study, with the article published in 2005 reporting results after the 24-month follow-up. Four studies were of fair quality and one was of poor quality (Broers et al 2005) – the population sample studied in the case series by Broers et al (2005)

had participated in a research project by the same authors published 3 years previously. The subpopulation of people with type 1 diabetes and hypoglycaemia unawareness was of particular interest for this question; however, no studies were found that fulfilled inclusion criteria in this search. One study of a population with impaired hypoglycaemia awareness was excluded because it was a pilot study with no power calculations (Thomas et al 2007).

The intervention 'self-study material' in Nordfeldt et al (2003) examined children with type 1 diabetes and their parents. Those in the intervention group (n=222) received two video programs consisting of interview clips of young patients and their parents regarding diabetes treatment and prevention of hypoglycaemia, including comments from a consultant physician diabetologist. A self-study brochure mailed out 1 month later contained frequently asked questions on aspects of severe hypoglycaemia management. The control group (n=110) were provided material as a video of general diabetes information and corresponding brochure. The yearly incidence of severe hypoglycaemia was obtained by postal surveys at baseline and 12 months later.

The three other studies examined the intervention, blood glucose awareness training (BGAT), with slight differences in edition and language. For example, in Schachinger et al (2005), the German version of BGATIII was delivered by a physician-psychologist team to groups of 5–12 participants in 8 weekly sessions, with each session lasting 2 hours. The sessions focused on internal cues, disruptions in cognitive and motor performance, and mood changes. Patients were taught to use these signals to recognise when their blood glucose level was too high or low. Exogenous cues such as insulin dose, food and exercise were reviewed subsequently. Weekly homework and preparatory readings were required. The control group participated in 3-monthly sessions by one physician; focus topics were set out, with participants determining the specific issues and timing. Further details of the study interventions and control methods are described in the technical document.

All studies reported a significant reduction in severe hypoglycaemia after intervention. The largest study, which was an RCT of fair quality, reported a reduction of severe hypoglycaemia in the intervention group compared with control. The difference in incidence of severe hypoglycaemia at 24 months between the two groups was -15% (95%CI: -1 to -29): there were 20 episodes of severe hypoglycaemia in the intervention group compared with 34 in the control group (Nordfeldt et al 2005). While the 12-month results of the same study showed no difference between intervention and control groups (95%CI: -4 to 24), a difference in change from baseline was seen in the intervention group (-15%, 95%CI: 1 to 29, $p=0.039$) but not the control group (+3%, 95%CI: -11 to 17) (Nordfeldt et al 2003). The RCT published by Schachinger et al (2005) reported that BGAT also led to a decrease in severe hypoglycaemia episodes, with a time-group interaction of $p=0.04$, and also a reduction in severe hypoglycaemia episodes per 6 months in the BGAT group compared to baseline ($p=0.0$). Change from post-exposure to baseline was also significant in the nonrandomised study by Broers et al (2005): the number of severe hypoglycaemia episodes decreased after intervention ($p=0.001$); there were 7.9 episodes per year at baseline reported in the BGAT group participants, and 1.7 at 12 months of follow-up. Cox et al (2001) reported that severe hypoglycaemia was reduced by about one-third across the first and last 6 months of follow-up compared with baseline ($p<0.002$), with mean episodes per month of 1.6 at baseline, 1.2 at 6 months and 1.1 at 12 months. As these case series by Broers et al (2005) and Cox et al (2001) did not have a control group, the observed change may not have been attributable to the intervention alone.

The populations recruited varied across the different studies, potentially affecting generalisability. The participants in the paediatric study by Nordfeldt et al (2003) were a

broad, nonselected population with type 1 diabetes, because all consenting subjects with paediatric type 1 diabetes in a defined geographic catchment area were recruited. In the RCT by Schachinger et al (2005), the selection of the population studied was biased towards those with a history of recurrent severe hypoglycaemia, who also had a longer diabetes duration and were older than is generally the case in a population with type 1 diabetes. Thus, the results of that study are most relevant to adults with type 1 diabetes who had previously experienced severe hypoglycaemia.

Evidence statement	
Q16.3	Level II and Level IV evidence shows that specific educational interventions (in particular, BGAT) reduce the rate of severe hypoglycaemia.
Recommendation	
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).
Practice points	
PP16.3.1	Developmentally appropriate structured education programs, such as 'self-study material' video programs and Blood Glucose Awareness Training (BGAT), can be used to help to reduce rates of severe hypoglycaemia.
PP16.3.2	Some programs, such as BGAT, can be delivered as individual or group programs.
PP16.3.3	Where resource constraints apply, structured education should be offered preferentially to individuals at highest risk of and from severe hypoglycaemia; for example, those with a history of recurrent severe hypoglycaemia, and adults who are motor vehicle drivers.
PP16.3.4	Research into modified programs to prevent severe hypoglycaemia that may require less resource and time input needs to be undertaken. Such research needs documented outcomes, including assessment of optimal time intervals for people to undertake refresher courses.
BGAT, blood glucose awareness training	

16.4 Efficacy and safety of hypoglycaemia treatments

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative contains information from contemporary evidence based guidelines developed by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Clarke et al 2009) and clinical consensus guidelines (Endocrinology Expert Group 2009; Ambler and Cameron 2010). The grades of evidence used in the ISPAD guidelines are shown in Chapter 2, Section 2.2.3 (Table 2.2).

Treatment for mild to moderate and severe hypoglycaemia is well established and effective for children and adults (Pearson 2008; Endocrinology Expert Group 2009). The amount of glucose needed to treat a hypo depends on the person's size, insulin plan, recent insulin doses and recent exercise. Bigger, older children and adults require the larger amount and occasionally more.

Treatment options for mild to moderate hypoglycaemia in a cooperative child includes 10-20g of oral glucose containing carbohydrate (Ambler and Cameron 2010), as:

- glucose tablets 10–20 g (not in children under 5 years)
- ordinary soft drink or cordial 125–250 mL
- fruit juice 125–250 mL
- sugar or honey (two to four teaspoons)
- jelly beans – 3 to 6 large or 6 to 12 small jelly beans (not in children under 5 years).

As a guide, smaller and younger children require the lower end of the 10-20 of carbohydrate to treat mild to moderate hypoglycaemia compared with larger and older children (Ambler and Cameron 2010).

In general, the initial therapy of rapidly digested and absorbed carbohydrate (above) is followed with a serve (eg 15g) of slower-acting carbohydrate, such as bread, milk, biscuits, apple or banana. However, this is not always required, particularly for those on CSII therapy. In a conscious yet uncooperative child where safe administration of adequate oral treatment is not possible, glucagon therapy, as described below, may be required.

Treatment of mild to moderate hypoglycaemia in adults may be addressed with readily available glucose containing food with 20-25g of carbohydrate. This should be promptly followed up by a food that has slower-acting carbohydrate such as a sandwich or dried fruit (Endocrinology Expert Group 2009). The amounts of carbohydrate recommended as a guide are based on studies showing that in adults, 20 g of oral glucose will raise the blood glucose level by 2.5-3.6 mmol/L (Wiethop and Cryer 1993). In contrast, recurrent over-treatment of mild hypoglycaemia with excess oral glucose should be avoided as it may contribute to unstable blood glucose and potentially, weight gain.

Severe hypoglycaemia in children who are not in hospital should be treated with glucagon subcutaneous (SC) or intramuscular (IM), as 0.5 mg (age less than 5 years), or 1 mg (age 5 years or more), given by the responsible parent or carer. Children with severe hypoglycaemia in hospital should initially be given 10% glucose at 2 mL/kg as an intravenous (IV) bolus, 0.45% sodium chloride with 5% glucose at maintenance rates to keep the blood glucose level above 4.0 mmol/L (Endocrinology Expert Group 2009; Ambler and Cameron 2010).

Severe hypoglycaemia occurring with unconsciousness in adults should be treated with glucagon 1 mg SC or IM, administered to patients by their partners or relatives; this is often also the choice of therapy used by paramedics. In the hospital setting, IV bolus glucose as 50%, 20–30 mL, is given through a secure cannula, then some form of maintenance glucose, such as 5% dextrose at 100 mL per hour, is often provided (Endocrinology Expert Group 2009). When glucagon is used to treat hypoglycaemia in children or adults, in subsequently conscious patients, some slower acting oral carbohydrate should subsequently be consumed to help replenish hepatic glycogen stores.

The methods described above to treat hypoglycaemia are highly efficacious in resolving symptoms of hypoglycaemia and returning blood glucose to the normal range. Following an episode of treated hypoglycaemia, the blood glucose should be measured 10-15 minutes afterwards to ensure it has returned to the normal range (Clarke et al 2009). If there is inadequate blood glucose response or an inadequate response, then oral intake of fast-acting glucose containing carbohydrate should be repeated, as described above; retesting the blood glucose in another 20–30 minutes should then occur to confirm that target glucose has been maintained and not exceeded.

Factors that may limit efficacy of treating moderate hypoglycaemia are if the glucose is not swallowed or if gastroparesis is present (e.g. due to diabetic gastroparesis in those with long-standing diabetes or intercurrent illness such as gastroenteritis). Even though gastric motility is stimulated during low blood glucose, in people with diabetic gastroparesis, gastric motility may not be normalised during hypoglycaemia (Kong and Horowitz 1999). In all cases of hypoglycaemia, close monitoring in follow-up is required, and the person should usually cease complex tasks or physical activity when moderate hypoglycaemia occurs, and instead focus on treating the moderate hypoglycaemia. The glucose provided orally as described

above would typically not be part of a mixed meal with significant amounts of fat, such as a chocolate bar, because the fat in the chocolate will reduce the rate of gastric emptying and, potentially, the rate of glucose absorption from the upper gastrointestinal tract (Kong and Horowitz 1999). In hypoglycaemia, autonomic symptoms of low blood glucose should begin to resolve within 5–15 minutes, and blood glucose should be above 4.0 mmol/L at 15 minutes or more after self-treatment. If symptoms and blood glucose have not improved, then a re-treatment of oral glucose may be required and possibly even parenteral therapy by glucagon, if there is concern that the oral glucose is not being absorbed.

In severe hypoglycaemia, the parenteral treatments are also typically highly efficacious, typically rapidly improving level of consciousness (Collier et al 1987; Namba et al 1993). However, it can take more than 60 minutes for the more subtle adverse cognitive effects of severe hypoglycaemia to fully resolve (Fanelli et al 2003). Glucagon administration is said to be underused as a versatile therapy for severe hypoglycaemia (Pearson 2008). Glucagon as therapy does require adequate glycogen stores to be present in the liver for glucagon to mobilise glucose from the glycogen, into the blood stream. Thus, in cases of prolonged fasting preceding severe hypoglycaemia, it would be predicted that glucagon would be less efficacious, and parenteral glucose would be the therapy of choice (Pearson 2008). In some cases, initial efficacy will be lost in severe hypoglycaemia after parenteral therapy, and this can occur, for example, if the insulin administered is much greater than physiological requirements. In such cases, re-treatment with IV bolus glucose may be required and higher rates of infusion and greater concentrations of glucose (e.g. in adults, up to 50% via a central vein site) may be required.

Side effects due to therapy for hypoglycaemia may also limit effectiveness. For example, glucagon often induces nausea and vomiting on regaining consciousness (Pearson 2008), and safe practice is to have the patient initially in the coma position before waking, and a vomit bag or bucket at the ready on its administration. Also, in severe hypoglycaemia, administration of 50% glucose IV is contraindicated in children, because it has been associated with contributing to death due to hyperosmolality (Endocrinology Expert Group 2009). As described above, to treat severe hypoglycaemia in children, 10% glucose only is recommended.

Once the episode of hypoglycaemia has been treated, it is important to carefully consider possible causes. Hypoglycaemia can often be explained by an imbalance between insulin type and dosage and lifestyle factors, such as carbohydrate intake and timing, and degree of physical activity (Cryer et al 2009). Any episode of severe hypoglycaemia should lead to a fundamental reassessment of the treatment regimen of the type 1 diabetes in the individual (Cryer et al 2009), including active involvement and consultation by the treating multidisciplinary health professional team to define, as far as possible, the precipitating and predisposing factors leading to the severe hypoglycaemia, to help prevent its recurrence. An adult driver who has experienced an episode of severe hypoglycaemia should not drive again until their medical carer has provided formal clearance to do so; in Australia, this will typically be the treating endocrinologist. Some insulin regimens, such as use of insulin analogues and continuous subcutaneous insulin infusion (CSII) pump therapy, may help to reduce the risk of severe hypoglycaemia in some cases. Nevertheless, it is the overall diabetes management package in intensive diabetes management, including lifestyle factors (e.g. diet and exercise) and blood glucose target setting and monitoring that will help to minimise the risk of hypoglycaemia events, including severe hypoglycaemia (Cryer et al 2009).

Changes in management that may be required after severe hypoglycaemia include target setting in blood glucose in the individual, modified physical activity and carbohydrate or alcohol intake, and varying insulin regimens (Cryer et al 2009). Closer attention to carbohydrate counting, and frequency and timing of blood glucose monitoring may also be required. Rarely, severe hypoglycaemia may also occur due to onset of new medical complications, which may induce hypoglycaemia in people with type 1 diabetes. Such complications include primary glucocorticoid deficiency of Addison's disease (primary cortisol deficiency) as described in an Australian paediatric case series (Thomas et al 2004). Although rare, Addison's disease is more common in people with type 1 diabetes; in Australia, it is most commonly caused by an autoimmune disease, and may present with hypoglycaemia, including in type 1 diabetes (Thomas et al 2004).

Some degree of 'impaired awareness of hypoglycaemia' is common in type 1 diabetes, with up to one-third of children and adults experiencing it (Ly et al 2011). Also known as 'hypoglycaemia unawareness', people with the condition typically do not readily detect the early warning (autonomic) symptoms of hypoglycaemia and they are at increased risk of developing severe hypoglycaemia (Cryer 2010). Reduced hypoglycaemia awareness increases in prevalence with diabetes duration and is thought to be a form of chronic autonomic failure related to type 1 diabetes (Cryer 2010; Ly et al 2011). In some cases, impaired awareness of hypoglycaemia may also develop after the occurrence of a single severe hypoglycaemia episode, and it may then resolve after 2-3 weeks of avoidance of hypoglycaemia (Cryer 2010; Ly et al 2011). Methods to help prevent severe hypoglycaemia in those with impaired awareness of hypoglycaemia include more frequent timing of blood glucose level checks and also treatment of any low capillary blood glucose levels (e.g. <4 mM), even in the absence of any symptoms of hypoglycaemia at the time of the low blood glucose occurring. In addition, blood glucose awareness training as reported in section 16.5, may have utility in preventing severe hypoglycaemia in those with impaired awareness, and real-time blood glucose monitoring with an in-built hypoglycaemia alarm in one recent Australian study improved counter-regulatory adrenaline responses to induced hypoglycaemia (Ly et al 2011).

In rare cases, despite the best efforts of all concerned, nonpreventable recurrent severe hypoglycaemia that is life-threatening occurs many times each year in a person with type 1 diabetes. The clinical scenario may be a person with more than 10 years of type 1 diabetes, who has hypoglycaemia unawareness and unstable diabetes with intercurrent end-organ complications, such as diabetic gastroparesis, which makes treatment of hypoglycaemia more difficult. Such patients could be formally assessed for forms of pancreas transplantation, including being enrolled in clinical trial programs of islet cell transplantation (Meloche 2007). While transplantation of the endocrine pancreas and related immunosuppression has its own inherent risks, it is recognised as a highly effective method to reduce the frequency of, or even abolish, recurrent life-threatening episodes of severe hypoglycaemia (O'Connell et al 2006).

16.4.1 Summary

While acute treatment of hypoglycaemia is usually highly effective, its therapy does differ somewhat in children and adults, including the doses of glucose and other agents used. Recurrent over treatment of mild hypoglycaemia should be avoided as it can contribute to unstable blood glucose and potentially, weight gain. In all cases of hypoglycaemia, occurrence should lead to consideration of the cause by the person with type 1 diabetes, in attempt to avoid recurrence. By the person with diabetes and their health care team identifying and managing risk factors for severe hypoglycaemia, including potentially

reversible factors, the occurrence of severe episodes may be minimised. In cases where severe hypoglycaemia has occurred, a fundamental reassessment of the type 1 diabetes treatment regimen is required to identify precipitating and predisposing factors that have contributed to the severe hypoglycaemia. The person with diabetes will need to work closely with the treating multidisciplinary diabetes care team of health professionals to reduce severe hypoglycaemia risk of recurrence.

While some insulin regimens, such as insulin analogues use and CSII pump therapy, may in some cases help to reduce severe hypoglycaemia risk, it is the overall diabetes management package, including lifestyle factors (such as diet, exercise) and blood glucose target setting and monitoring, that will help to minimise the risk of hypoglycaemia events including severe hypoglycaemia.

In people with a lack of hypoglycaemia awareness or 'hypoglycaemia unawareness', specific education programs to help regain symptoms of hypoglycaemia and to reduce further severe hypoglycaemia may be implemented and should be considered. In rare cases of nonpreventable recurrent severe hypoglycaemia, referral for assessment for pancreas transplantation – either the whole organ or islet cell transplantation – should be considered.

17 Acute complications – diabetic ketoacidosis and sick-day management

Diabetic ketoacidosis (DKA) is a life-threatening acute complication of type 1 diabetes. Treatment of patients with DKA uses significant health-care resources, and accounts for one out of every four dollars spent on direct medical care for adult patients with type 1 diabetes in the United States (Umpierrez and Kitabchi 2003). The mortality rate for DKA is less than 5% (Nyenwe et al 2010), but higher rates are observed in elderly patients and those with concomitant life-threatening illnesses. Infection is the most common precipitating cause for DKA, present in up to half of all cases, with urinary tract infection and pneumonia accounting for most infections. Other precipitating causes include surgery, trauma, myocardial ischaemia, psychological stress, and noncompliance or omission of insulin therapy.

Successful treatment of DKA requires frequent monitoring of the patient; fluid replacement and insulin to correct hypovolaemia, acidosis and hyperglycaemia; replacement of electrolyte losses; and careful investigation to determine the precipitating cause. Since most DKA cases occur in patients with a known history of diabetes, DKA should be largely preventable through frequent monitoring of blood glucose (BG) levels, early detection of ketosis and adequate replacement of insulin, together with education of patients, health-care professionals and the general public. The frequency of hospitalisations for DKA decreased following implementation of diabetes education programs, improved follow-up care and access to medical advice.

This chapter addresses the effectiveness of blood ketone monitoring for preventing DKA. Management of sick days and DKA are covered in Sections 17.3 and 17.4, below.

17.1 Ketone monitoring

Question 17.1

Does ketone monitoring prevent ketoacidosis or hospital admission?

The detailed systematic review of this question is in Chapter 17 of the accompanying technical report, and the evidence matrix is in Section C17 of Appendix C

Ketone monitoring is used at times of hyperglycaemia for the detection of severe insulin deficiency in the diagnosis of DKA, and to guide insulin replacement during sick days. Ketone bodies can be measured in two ways: from beta-hydroxybutyrate (β -OHB) in capillary blood samples, or from acetoacetic acid measured by a urine dipstick test. Quantitative measurement of β -OHB, the major circulating ketone during DKA, is positively correlated with the degree of acidosis in patients with DKA (Sheikh-Ali et al 2008; Turan et al 2008). Evidence suggests that β -OHB correlates better with changes in acid–base status than acetoacetate during the course of treatment for DKA (Laffel 1999). Capillary β -OHB is more sensitive than urinary ketone levels for detecting ketosis (Turan et al 2008). A systematic review examined the effectiveness of blood ketone monitoring versus urine ketone monitoring in preventing DKA or hospital admission.

The systematic review identified no Level I studies and one Level II study (Laffel et al 2006). Laffel et al (2006) was a prospective, two-centre study that assessed sick-day management using blood β -OHB monitoring compared with traditional urine ketone testing. Participants

(n=123, aged 3–22 years) were randomised to receive either a BG monitor that also measured blood β -OHB, or a monitor plus urine ketone strips. Participants were encouraged to check ketones during acute illness or stress, when glucose levels were consistently elevated (≥ 13.9 mmol/L on two consecutive readings), or when symptoms of DKA were present. After 6 months, participants in the blood ketone group checked ketones significantly more during sick days (91%) than participants in the urine ketone group (61%, $p < 0.001$). The incidence of hospitalisation and emergency assessment was lower in the blood ketone group (38/100 person years) than in the urine ketone group (75/100 person years, $p = 0.05$). Blood ketone monitoring during sick days appeared acceptable to, and was preferred by, young people with type 1 diabetes. The authors concluded that routine implementation of blood β -OHB monitoring for managing sick days and impending DKA could potentially reduce hospitalisation and emergency assessment compared with urine ketone testing.

The evidence for the effectiveness of blood ketone monitoring versus urine ketone monitoring for preventing DKA or hospital admission is therefore based on one randomised controlled trial with a low risk of bias. No studies were found in adults older than 22 years. The study was conducted in the United States, which has a well-developed health-care system; therefore, the results are applicable to the Australian health-care setting.

The study did not examine cost effectiveness, although there is level II evidence in children for cost effectiveness of blood vs urine ketone monitoring in management of DKA (Vanelli et al 2003).

Evidence statement	
Q17.1	Blood ketone measurement compared with urine ketone measurement, as part of a sick-day management plan, reduces the rate of emergency presentations and hospitalisations.
Recommendation	
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade C).
Practice points	
PP17.1	Blood ketone measurement is preferred, because it gives a more timely result. However, where blood ketone measurement is not available, urine ketone measurement is the alternative test as part of a comprehensive sick-day management plan.
PP17.2	Blood ketone measurement is preferred in people using CSII.
PP17.3	Blood ketone measurement may be especially useful in very young children or when urine specimens are difficult to obtain.
PP17.4	A comprehensive sick-day management plan should include written guidelines and 24-hour access to clinical advice.
PP17.5	The sick-day management plan should be regularly reviewed by the patient and diabetes health-care professional.
β -OHB, beta-hydroxybutyrate; CSII, continuous subcutaneous insulin infusion	

17.2 Sick-day management

This section was not systematically reviewed and as such no recommendations or practice points are made. The narrative contains information from contemporary evidence based guidelines developed by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Brink et al 2009). The grades of evidence used in the ISPAD guidelines are shown in Chapter 2, Section 2.2.3 (Table 2.2).

People whose diabetes is well controlled generally do not experience more illness or infections than those without diabetes (Brink et al 2009), although there is some evidence of impaired leukocyte function in poorly controlled diabetes (Bagdade et al 1974). Some illnesses, particularly those associated with fever, raise BG levels because of higher levels of stress hormones promoting gluconeogenesis and insulin resistance, while ketone body production increases due to relative or absolute insulin deficiency. Illness associated with vomiting and diarrhoea (e.g. gastroenteritis) may lower BG levels and result in hypoglycaemia rather than hyperglycaemia. Decreased food intake, poor absorption and slower emptying of the stomach during gastroenteritis may also contribute to hypoglycaemia. Insulin requirements are sometimes increased during the incubation period of an infection for a few days before the onset of the illness. The increased need for insulin may persist for a few days after the illness has passed, due to insulin resistance.

17.2.1 Sick-day management principles

The following principles should be considered in the management of sick days for a child, adolescent or adult with type 1 diabetes (Brink et al 2009).

- **More frequent monitoring:**
 - BG levels should be monitored regularly, initially every 2 hours, particularly if ketones are present.
 - Urinary or fingerprick blood ketone tests help to guide sick-day management. Ketone testing should always be performed if the BG level is above 15 mmol/L.
- **Do not stop insulin:**
 - Insulin doses may need to be increased or decreased, depending on the illness.
 - If the BG level is above 15 mmol/L and ketones are increased, additional rapid or short-acting insulin is needed. The dose and frequency of injection will depend on the level and duration of hyperglycaemia, and the severity of ketosis.
 - If there is hyperglycaemia with negative or small amounts of ketones, an additional 5–10% of total daily dose (TDD) (or 0.05–0.1 U/kg) should be given as rapid or short-acting insulin. This may be repeated every 2–4 hours based on results of BG level monitoring; see Table 17.1, adapted from ADEA guidelines (ADEA 2006) and Ambler and Cameron (2010).
 - If there is hyperglycaemia and more marked ketonaemia or ketonuria (moderate to high), an additional 10–20% of TDD (usually not more than 0.1 U/kg) may need to be given as rapid or short-acting insulin. This dose should be repeated every 2–4 hours; based on frequent BG levels and ketone results.
 - People on continuous subcutaneous insulin infusion (CSII) use only rapid-acting insulin; therefore, DKA can develop rapidly. Episodes of hyperglycaemia must be taken seriously, especially if associated with positive urine or blood ketones (or

both). Correction doses should be given through the pump if there are no ketones or with a syringe or pen injection if ketones are present.

- **Maintain hydration:**

- Hyperglycaemia, fever, excessive glycosuria and ketonuria increase fluid losses.
- Elevated levels of ketones, whether associated with low BG (starvation) or high BG (insulin deficiency), contribute to nausea and vomiting, leading to decreased food and fluid intake, further elevated levels of ketones, and dehydration and ketoacidosis.
- Liquids for hydration should contain salt and water and not just plain water if there are ongoing losses due to vomiting or diarrhoea.
- In young children with diabetes, intravenous (IV) fluids may be required if nausea, vomiting or diarrhoea are persistent.
- When vomiting occurs in a person with diabetes, it should always be considered a sign of insulin deficiency until proven otherwise.

- **Treat the underlying illness:**

- The underlying illness should be treated as it would be for a person without diabetes.

Table 17.1 Guidelines for sick day management

Blood glucose level (mmol/L)	Ketones – blood (mmol/L) ^a or urine	Supplemental insulin dose (can be given up to 2 hourly) ^b	Timing of review	Fluid intake
<4.0	<1.0 Negative	Insulin dose reduction may be required. Consider mini dose glucagon to prevent hypoglycaemia if vomiting, diarrhoea or reduced carbohydrate intake	Check every 20–30 minutes until BGL >4. Supervised medical care required if ketones remain positive and BGL remains low	Take sweetened fluids or quick-acting carbohydrate (or both); hospital admission for IV fluids may be needed if BGL cannot be maintained.
	≥1.0 Positive	Priority is to increase BGL with fluid and carbohydrate		
4–8	< 1.0 Negative/ trace	No change to insulin	Two hourly	Give sweetened fluids or extra carbohydrate to maintain or increase BGL
	1.0–1.4 Small	No change to insulin. Ketones indicate carbohydrate and insulin deficiency.	Two hourly	
	>1.5 Moderate/ Large	5% supplemental insulin may be required	Two hourly	
8–15	<1.0 Negative/ trace	May fall without extra insulin. If persistently elevated, consider 5 % supplemental insulin	Two hourly	Sweetened fluids recommended
	1.0–1.4 Small	If persistently elevated ketones, consider 5–10% supplemental insulin	Two hourly	
	>1.5 Moderate/ large	10% supplemental insulin dose	Hourly	
>15	<1.0 Negative/ trace	5–10% supplemental insulin dose	Hourly	Unsweetened fluids recommended
	1.0–1.4 Small	10–15% supplemental insulin dose	Hourly	
	>1.5 Moderate/ large	15–20% supplemental insulin dose	Hourly	

BGL, blood glucose level; IV, intravenous

^a blood 3β-hydroxybutyrate

^b Refers to percentage of total daily insulin dosage given as rapid or fast-acting supplemental insulin dose. Exercise caution with supplemental insulin doses in the presence of BGL <8 mmol/L – advise increasing sweetened fluid intake first.

17.3 Diabetic ketoacidosis

This section was not systematically reviewed and as such no recommendations or practice points are made. The narrative contains information from evidence based guidelines developed by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (Wolfsdorf et al 2009) and the American Diabetes Association (Kitabchi et al 2006). The grading of evidence used in these guidelines is shown in Chapter 2, Section 2.2.3 (Tables 2.2 and 2.3).

17.3.1 Background

DKA is characterised by the triad of uncontrolled hyperglycaemia, metabolic acidosis and increased total body ketone concentration. DKA results from absolute or relative deficiency of circulating insulin, and the effects of increased levels of the counter-regulatory hormones (i.e. catecholamines, glucagon, cortisol and growth hormone) (Foster and McGarry 1983; Kitabchi et al 2006). The combination of low serum insulin and high counter-regulatory hormone concentrations causes an accelerated catabolic state, with increased glucose production by the liver and kidneys, and impaired peripheral glucose use. This leads to hyperglycaemia, hyperosmolality, increased lipolysis and ketogenesis, causing hyperketonaemia and metabolic acidosis. Hyperglycaemia and hyperketonaemia cause osmotic diuresis, dehydration and loss of electrolytes, which often is aggravated by vomiting. If these metabolic derangements are not arrested and corrected with exogenous insulin and fluid and electrolyte therapy, then fatal dehydration and metabolic acidosis will ensue. Ketoacidosis may be aggravated by lactic acidosis from poor tissue perfusion or sepsis.

Patients with DKA have severe depletion of water and electrolytes from both the intracellular and extracellular fluid compartments. Despite their dehydration, patients continue to maintain normal blood pressure, and have considerable urine output until extreme volume depletion and shock occurs, leading to a critical decrease in renal blood flow and glomerular filtration. At presentation, the magnitude of specific deficits in an individual patient varies depending on the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high carbohydrate content exacerbate the hyperglycaemia.

DKA at diagnosis is more common in younger children (<5 years of age), and in children whose families do not have ready access to medical care for social or economic reasons. The risk of DKA in established type 1 diabetes is 1–10% per patient per year (Wolfsdorf et al 2009). The risk of DKA is increased in people with poor glycaemic control or previous episodes of DKA; peripubertal and adolescent girls; children with psychiatric disorders, including those with eating disorders; children with difficult or unstable family circumstances and children with limited access to medical services. The risk of DKA is also increased in people who omit insulin or use CSII (because only rapid insulin is used); interruption of insulin delivery for any reason rapidly leads to insulin deficiency.

17.3.2 Definition of diabetic ketoacidosis

The biochemical criteria for the diagnosis of DKA are:

- hyperglycaemia (BG level >11 mmol/L)
- venous pH <7.3 or bicarbonate <15 mmol/L
- ketonaemia and ketonuria.

17.3.3 Management

Consensus guidelines for managing DKA have been published elsewhere; the guidelines below are adapted from these (Dunger et al 2004; Kitabchi et al 2006; Wolfsdorf et al 2009).

Successful management of DKA requires meticulous monitoring of the patient's clinical and biochemical response to treatment, thereby enabling timely adjustments in treatment when indicated by the patient's clinical or laboratory data. Clinical observations, IV and oral medications, fluids and laboratory results should be documented on a flow chart each hour. People of all ages with severe DKA should receive care in an intensive care unit or comparable high-intensity unit. In DKA, timely rehydration and correction of the acidosis and electrolyte disturbances are priorities in care (Kitabchi et al 2006). Children and adolescents with DKA should be managed in a unit that has (Wolfsdorf et al 2009):

- experienced nursing staff trained in monitoring (of vital signs and neurological status) and management
- a paediatric endocrinologist, consultant paediatrician or paediatric critical care specialist with training and expertise in the management of DKA, who can direct inpatient management; where such expertise is not available onsite, telephone advice should be sought from the appropriate specialists
- access to laboratories for frequent and timely evaluation of biochemical variables
- written guidelines for DKA management in young people

A. Emergency assessment

- Perform a clinical evaluation to confirm the diagnosis and determine its cause. Look for evidence of infection.
- Weigh the patient and use this weight for calculations.
- Assess clinical severity of dehydration.
- Assess level of consciousness (using the Glasgow coma scale).
- Obtain a blood sample for laboratory measurement of serum or plasma glucose; electrolytes (including bicarbonate or total carbon dioxide [CO₂]); blood urea nitrogen; creatinine; osmolality; venous (or arterial in critically ill patient) pH; pCO₂; full blood count; and calcium, phosphorus and magnesium concentrations.
- Perform a urinalysis or blood test for ketones (or point-of-care measurement on a fingerprick blood sample using a bedside meter if available). There is some evidence that serum β -OHB levels >3.0 mmol/L in children and >3.8 mmol/L adults are more reliable measures of DKA than serum bicarbonate (Sheikh-Ali et al 2008).
- Obtain appropriate specimens for culture (blood, urine or throat) and consider performing a chest X-ray to exclude infection, unless there is a clear alternative explanation for the DKA.
- If laboratory measurement of serum potassium is delayed, perform an electrocardiogram for baseline assessment of potassium status (see details of electrocardiographic [ECG] features below under section E, below).

B. Supportive measures

- Secure the airway and empty the stomach by continuous nasogastric suction, to prevent pulmonary aspiration in the unconscious or severely obtunded patient.

- Insert a peripheral IV catheter for convenient and painless repetitive blood sampling.
- Use a cardiac monitor for continuous electrocardiographic monitoring to assess T-waves for evidence of hyperkalaemia or hypokalaemia.
- Give oxygen to patients with severe circulatory impairment or shock.
- Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- Catheterise the bladder if the patient is unconscious or unable to void on demand (e.g. in infants and very ill young children).

C. Fluid replacement

- For patients who are severely volume depleted but not in shock, begin resuscitation immediately with 0.9% saline, to restore the peripheral circulation.
 - The volume and rate of administration depends on circulatory status; where clinically indicated, the volume administered for children is typically 10 mL/kg/hour over 1–2 hours, and may be repeated if necessary. For adults, 1 L stat, followed by a second 1 L of 0.9% saline during the first hour is a typically used (Kitabchi et al 2006).
- In the rare patient with DKA who presents in shock, rapidly restore circulatory volume with isotonic saline. For children, administer 20 mL/kg boluses, infused as quickly as possible through a large bore cannula, with reassessment after each bolus.
 - Intraosseous access should be considered after multiple attempts to gain IV access have failed.
 - Fluid management (maintenance plus deficit replacement) should be with 0.9% saline for at least 4–6 hours. Thereafter, deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride, potassium phosphate or potassium acetate (see below under potassium replacement).
 - The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 hours. A method for calculation of maintenance fluids is shown in Table 17.2. Fluid volumes for the subsequent phase of rehydration are shown in Table 17.3.

Example

- A 6-year-old boy weighing 20 kg, who is assessed as 10% dehydrated, will be given maintenance fluids of 1500 mL per 24 hours and rehydration fluids of $10 \times 10\% \times 20\text{kg}$ (2000 mls) over 48 hours, or a total volume of 2500 mL per 24 hours for 2 days.

Table 17.2 Calculation of maintenance fluid requirements of children by weight

Patient age / weight	Daily IV requirements	Hourly IV requirements
3 to 10kg	100 mL/kg	4.0 mL/kg
>10 – 20kg	$1000 + 50 \times [\text{wt}(\text{kg}) - 10]$ mLs	$40 + 2 \times [\text{wt}(\text{kg}) - 10]$ mLs
>20kg	$1500 + 20 \times [\text{wt}(\text{kg}) - 20]$ mLs	$60 + 1 \times [\text{wt}(\text{kg}) - 20]$ mLs

- After initial resuscitation, and assuming 10% dehydration, the total fluid volume should be given over 48 hours. Table 17.3 gives volumes for maintenance and rehydration per 24 hours and per hour. If fluid has been given for resuscitation, this volume *should not* be subtracted from the amount shown in the table. Fluids given orally (when patient has improved) should be subtracted from the amount in the table below

Table 17.3 Example of fluid volumes for the subsequent phase of rehydration

Body weight (kg)	Maintenance fluids	DKA: Give maintenance fluids <i>plus</i> 5% of body weight per 24 hours	
	Infusion rate (mL/24 hours)	Infusion rate (mL/24 hours)	Infusion rate (mL/hour)
4	400	600	25
5	500	750	31
6	600	900	38
7	700	1050	44
8	800	1200	50
9	900	1350	56
10	1000	1500	63
11	1050	1600	67
12	1100	1700	71
13	1150	1800	75
14	1200	1900	79
15	1250	2000	83
16	1300	2100	88
17	1350	2200	92
18	1400	2300	96
19	1450	2400	100
20	1500	2500	104
22	1540	2640	110
24	1580	2780	116
26	1620	2920	122
28	1660	3060	128
30	1700	3200	133
32	1740	3340	139
34	1780	3480	145
36	1820	3620	151
38	1860	3760	157
40	1900	3900	163
45	2000	4250	177
50	2100	4600	192
55	2200	4950	206
60	2300	5300	221
65	2400	5650	235
70	2500	6000	250
75	2600	6350	265
80	2700	6700	279

- The severity of dehydration may be difficult to determine and is frequently underestimated or overestimated; therefore, infuse fluid each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age, weight or body surface area.
- Do not routinely add urinary losses to the calculation of replacement fluid, although this may be advisable in rare circumstances.
- When oral fluid is tolerated, reduce IV fluid so that the total amount of fluid given to the patient per hour does not exceed the calculated hourly rehydration volume.

- The sodium content of the fluid may need to be increased if measured serum sodium is low and does not rise appropriately as the plasma glucose concentration falls.
- For adults, the subsequent approach to fluid replacement is similar to that used in children. If hypernatraemia occurs in adults, then changing the hydration fluid to 0.45% saline is appropriate (Kitabchi et al 2006).

D. Insulin therapy

- Start insulin infusion after the patient has received initial volume expansion.
- Correct insulin deficiency as follows:
 - **Dose:** 0.1 unit/kg/hour (e.g. dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit=1 mL).
 - **Route of administration:** An IV bolus is unnecessary in children and should not be used at the start of therapy. In adults, an IV bolus of insulin at 0.1 IU/kg of body weight is recommended in some DKA protocols (Kitabchi et al 2006).
- In general, keep the dose of insulin at 0.1 unit/kg/hour, at least until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L or closure of the anion gap); this invariably takes longer than normalisation of blood glucose concentrations.
- If the patient demonstrates marked sensitivity to insulin (e.g. some young children with DKA and patients with hyperglycaemic hyperosmolar state), the dose may be decreased to 0.05 unit/kg/hour or less, provided that metabolic acidosis continues to resolve.
- During initial volume expansion, the plasma glucose concentration falls steeply. Thereafter, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/hour, depending on the timing and amount of glucose administration.
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycaemia, add 5% glucose to the IV fluid (e.g. 5% glucose in 0.45% saline) when the plasma glucose falls to 15 mmol/L, or sooner if the rate of fall is precipitous.
- If necessary, use 7.5–10% dextrose to prevent hypoglycaemia while continuing to infuse insulin to correct the metabolic acidosis.
- If BG falls very rapidly (>5 mmol/L/hour) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 15 mmol/L.
- If biochemical parameters of DKA (pH and anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (e.g. infection or errors in insulin preparation). In adults, in nonresponding cases, a doubling of the hourly insulin administration amount as a bolus may be indicated each hour to reverse the acidosis (Kitabchi et al 2006).

E. Potassium replacement

- Potassium-replacement therapy is required for DKA therapy. This is because a total body deficit of potassium occurs in DKA and correction of the acidosis in the absence of potassium therapy will usually rapidly make this apparent through the development of hypokalaemia. Patients may have hyperkalaemia, hypokalaemia or normokalaemia at presentation, depending on the total body potassium deficit and the degree of acidosis.
- If the person is hypokalaemic, this indicates a severe deficit of total body potassium. Start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion and

concurrent with starting insulin therapy. If the patient is hyperkalaemic, defer potassium replacement therapy until urine output is documented.

- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the patient has hyperkalaemia or hypokalaemia. Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalaemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalaemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement is based on serum potassium levels. If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.
- Potassium phosphate may be used together with potassium chloride or acetate (e.g. 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate, or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate).
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum rate of IV potassium replacement is usually 0.5 mmol/kg/hour.
- If hypokalaemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

F. Phosphate

- Prospective studies have not shown clinical benefit from phosphate replacement.
- Severe hypophosphataemia accompanied by unexplained weakness should be treated.
- Potassium phosphate may be safely used as an alternative to, or combined with, potassium chloride or acetate, provided serum calcium is monitored carefully to avoid hypocalcaemia.

G. Acidosis

- Progressive monitoring and correction of acidosis is a key element of care in DKA. In adults with DKA, acidosis is the main factor that lowers consciousness (Nyenwe et al 2010).
- The metabolic acidosis in DKA will usually resolve with the treatment regimen of rehydration and insulin therapy.
- Bicarbonate therapy may cause a paradoxical brain acidosis, and its administration is not recommended unless the acidosis is profound and likely to affect adversely the action of adrenaline (epinephrine) during resuscitation.
- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes.

H. Introduction of oral fluids and transition to subcutaneous insulin injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis or ketosis may still be present).
- When oral fluid is tolerated, IV fluid should be reduced.
- To prevent rebound hyperglycaemia, the first subcutaneous injection should be given 15–30 minutes (with rapid-acting insulin) or 1–2 hours (with regular insulin) before ceasing the insulin infusion, to allow sufficient time for the insulin to be absorbed. With intermediate-acting or long-acting insulin, the overlap should be longer and the IV

insulin gradually lowered. For example, for the patient on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion stopped the next morning.

I. Cerebral oedema

This complication of DKA therapy is a major concern in children.

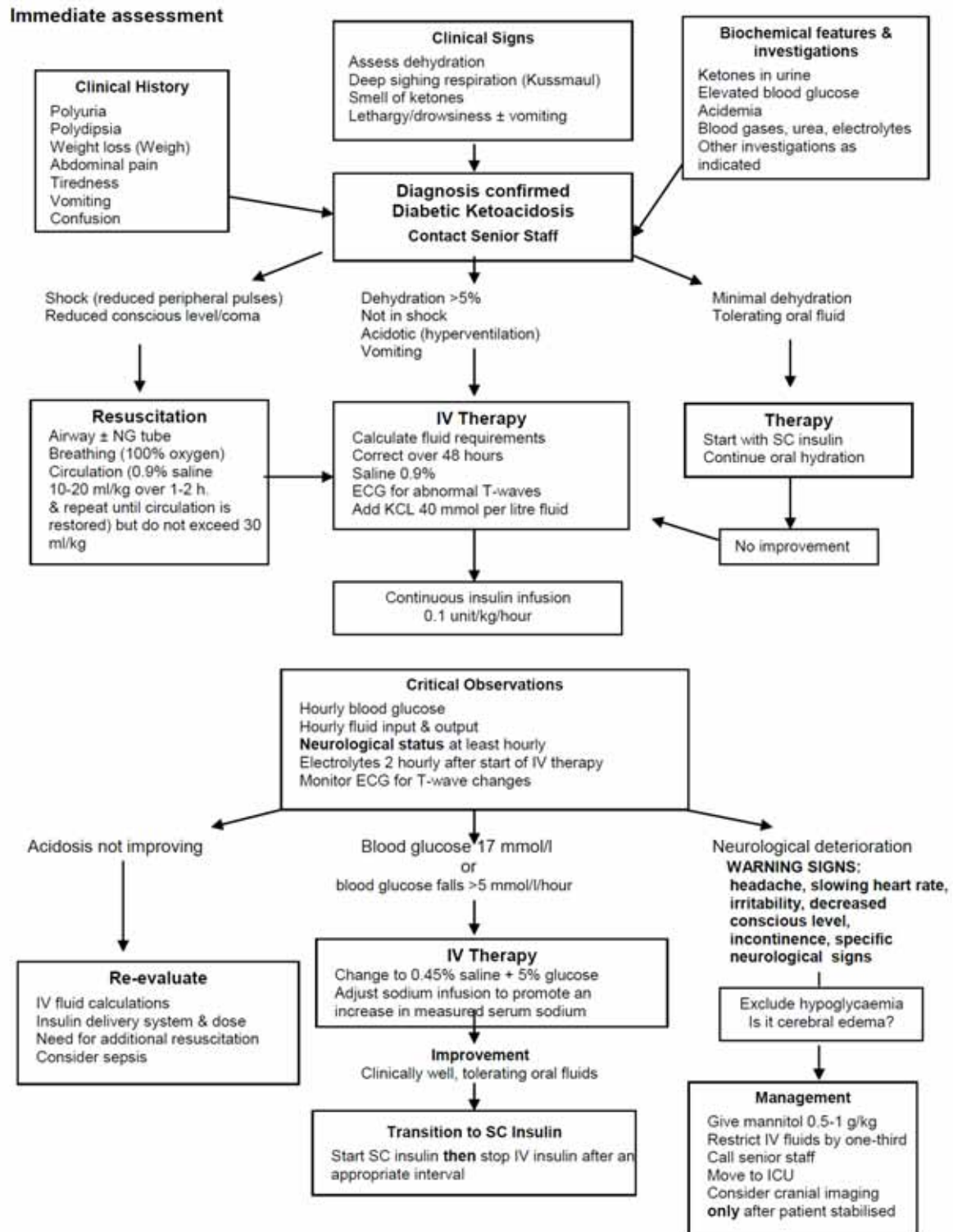
- **Warning signs and symptoms of cerebral oedema include:**
 - headache and slowing of heart rate
 - change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
 - specific neurological signs (e.g. unreactive pupils or cranial nerve palsies)
 - rising blood pressure
 - decreased O₂ saturation.
- **Treatment of cerebral oedema:**
 - Initiate treatment as soon as the condition is suspected.
 - Reduce the rate of fluid administration by one-third.
 - Give mannitol 0.5–1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours.
 - Consider using hypertonic saline (3%), 5 mL/kg over 30 minutes, as an alternative to mannitol, especially if there is no initial response to mannitol.
 - Make sure that mannitol or hypertonic saline is available at the bedside.
 - Elevate the head of the bed.
 - Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO₂ <2.9 kPa [22 mmHg]) has been associated with poor outcomes and is not recommended.
 - After treatment for cerebral oedema has been started, take a cranial computed tomography scan to rule out other possible intracerebral causes of neurologic deterioration (≈10% of cases), especially thrombosis or haemorrhage, which may benefit from specific therapy.

17.3.4 Summary

DKA is caused by either relative or absolute insulin deficiency. It is preferable for patients with DKA to be managed in centres experienced in its treatment, where vital signs, neurological status and laboratory results can be monitored frequently. Fluid replacement should begin before insulin therapy is started. Volume expansion (resuscitation) is required only if needed to restore peripheral circulation. Subsequent fluid administration (including oral fluids) should rehydrate evenly over 48 hours at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement. The usual starting dose of insulin therapy is 0.1 U/kg/hour, 1–2 hours after starting fluid replacement therapy.

There is no single generally recommended algorithm to manage DKA in adults. For a consensus approach algorithm in managing DKA in adults from the American Diabetes Association, see Kitabchi et al (2006).

Figure 17.1 Algorithm for managing diabetic ketoacidosis in children and adolescents (Wolfsdorf et al 2009)



18 Microvascular and macrovascular complications

The long-term vascular complications of diabetes include retinopathy (leading to visual impairment and blindness), nephropathy (resulting in hypertension and renal failure), neuropathy (manifesting as pain, paraesthesiae, muscle weakness and autonomic dysfunction) and macrovascular disease (cardiac disease, peripheral vascular disease and cerebrovascular disease). Although clinical evidence of microvascular and macrovascular complications is uncommon in childhood and adolescence, early functional and structural abnormalities may be present a few years after the onset of type 1 diabetes (Cho et al 2011).

It is now more than 18 years since the Diabetes Complications and Control Trial (DCCT) provided clear evidence that intensive diabetes treatment and improved glycaemic control significantly reduce the risk of microvascular complications compared with conventional treatment. The follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated a continued benefit for randomised groups, together with a risk reduction for macrovascular disease. In parallel with changes in clinical treatment goals and management, for example increased use of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), identification of risk factors, regular complication screening and more aggressive treatment of early abnormalities, there is evidence for a declining incidence of some complications, such as retinopathy, in young people (Mohsin et al 2005) and adults (Nathan et al 2009) with type 1 diabetes.

18.1 Effect of intensive glycaemic management on complications

Question 18.1

What is the effect of intensive glycaemic management on microvascular and macrovascular complications?

The detailed systematic review of this question is in Chapter 18 of the accompanying technical report, and the evidence matrix is in Section C18 of Appendix C

This section addresses the effects of intensive glycaemic control (referred to here as intensive management), as implemented by the DCCT study. Intensive glycaemic control was defined in that study as the maintenance of glycaemic control as close as possible to the normal range. As described in detail in Chapter 5, the DCCT and its epidemiological follow-up – the EDIC study – demonstrated that a management program of intensive blood glucose control reduced the microvascular and macrovascular end-organ complications of diabetes (DCCT Research Group 1993). The systematic literature review provided further support for the effects of an intensive treatment strategy (see Chapter 18 of the technical report) on these outcomes and identified a meta-analysis of microvascular outcomes (Wang et al 1993a) and two meta-analyses of macrovascular disease that included data from the DCCT/EDIC (Lawson et al 1999; Stettler et al 2006).

18.1.1 Microvascular complications

As described in Chapter 5, data from the DCCT indicated that new onset and progression of diabetic retinopathy, nephropathy, and peripheral and autonomic neuropathy were reduced by intensive treatment compared with conventional treatment (DCCT Research Group 1993). The observational data showed that, for every 1.0% unit decrease in glycated haemoglobin

(HbA_{1c}), there was a 39% decrease in retinopathy risk over the range of HbA_{1c} values studied. For nephropathy, for every 1.0% unit decrease in HbA_{1c}, there was a 25% decrease in the risk of microalbuminuria. For each microvascular outcome, no glycaemic threshold for risk reduction was detected above the nondiabetic range of HbA_{1c}.

A meta-analysis that preceded the DCCT identified 16 studies with duration of follow-up ranging from 8 to 60 months (Wang et al 1993a). Most of the studies included people with normal albumin excretion or microalbuminuria and normal serum creatinine at baseline. All but one of these studies achieved better or near normal glycaemic control with intensive treatment. The between-group difference in HbA_{1c} by study end was -1.4% (95% confidence interval [CI]: -1.8 to -1.1).

After 2–5 years of intensive treatment, the risk of retinopathy progression was significantly reduced (odds ratio [OR] 0.49, 95%CI: 0.28 to 0.85, $p=0.01$), and there was no heterogeneity across pooled studies ($p=0.89$). Progression to background retinopathy is clinically different from progression to proliferative retinopathy. Therefore, some studies also reported these outcomes separately, noting that intensive treatment significantly slowed retinopathy progression to more severe states, such as proliferative retinopathy, or changes requiring laser treatment (OR 0.44, 95%CI: 0.22 to 0.87, $p=0.02$) without heterogeneity ($p=0.99$). For nephropathy, intensive treatment significantly reduced the risk of nephropathy progression (OR 0.34, 95%CI: 0.2 to 0.58, $p<0.001$) without heterogeneity ($p=0.99$).

18.1.2 Macrovascular complications

A meta-analysis examined six randomised controlled trials (RCTs), each running for more than two years, from which data on cardiovascular events were pooled (Lawson et al 1999). With 1732 participants, the number of first major macrovascular events was reduced, with a relative risk ratio (RRR) of 0.55 (95%CI: 0.35 to 0.88, $p=0.02$), but not the number of patients developing macrovascular disease. Given that the risk of a macrovascular event is highest in those who have already had one event, the benefit of intensive therapy over conventional therapy on the number of macrovascular events, but not on the number of patients, suggests that intensive therapy decreases the likelihood of a patient having multiple types of events. In 2006, this was updated with another meta-analysis of data from 1800 people with type 1 diabetes. The total number of recorded events was small: 134 events in 11 293 person-years (Stettler et al 2006). Nevertheless, the risk of any macrovascular event (RRR 0.38, 95%CI: 0.26 to 0.56), cardiac event (RRR 0.41, 95%CI: 0.19 to 0.87) or peripheral vascular event (RRR 0.39, 95%CI: 0.25 to 0.62) was significantly reduced, while the risk of cerebrovascular events was not significantly reduced (Stettler et al 2006). Assuming a typical incidence of one macrovascular event per 100 person years, 16 patients would need to receive intensified treatment for 10 years to prevent one macrovascular event (Stettler et al 2006). The DCCT was included in the 1999 macrovascular meta-analysis, and the DCCT and EDIC were included in the 2006 macrovascular meta-analysis. The systematic reviews found no heterogeneity in the findings of the six RCTs (Lawson et al 1999) or the eight RCTs (Stettler et al 2006) examining macrovascular outcomes in type 1 diabetes. In both those meta-analyses, data from the DCCT and EDIC dominated the participant numbers examined.

18.1.3 Glycaemic control

The intensive glycaemic control approach in the DCCT aimed to maintain blood glucose concentrations close to the normal range while preserving clinical wellbeing, as defined by the conventional or standard treatment group (DCCT Research Group 1993). The blood glucose targets are detailed in Chapter 5. The intensive treatment methods across each study included in the meta-analyses used a similar intensive treatment approach to the

DCCT and EDIC. The consistent key elements of intensive treatment were the frequency of insulin treatment administration, the frequency of self-monitored blood glucose and the provision of strong support from a coordinated multidisciplinary team of health professionals. The support included frequent contact with diabetes educators, dieticians, psychologists and social workers, as well as with endocrinologists skilled in intensified management. Processes included frequent study centre visits, telephone contacts each month, and even more frequent contact by telephone for review and dose adjustment. In the DCCT, quality of life was maintained in the intensive treatment group when assessed by questionnaire, compared with the conventional group.

18.1.4 Adverse events

A fair-quality Level I study (Egger et al 1997a) examined the adverse events associated with this intensity of glucose control in terms of severe hypoglycaemia, diabetic ketoacidosis (DKA) and death. Fourteen RCTs were identified that contributed 16 comparisons, with a total of 1028 patients allocated to intensified treatment and 1039 patients allocated to conventional treatment. A total of 26 patients died, 846 suffered at least one episode of severe hypoglycaemia, and 175 experienced DKA. The pooled OR for hypoglycaemia was 2.99 (95%CI: 2.45 to 3.64). The risk of DKA depended on the type of intensified treatment used; the OR was 7.20 (95%CI: 2.95 to 17.58) for exclusive use of pumps; 1.13 (95%CI: 0.15 to 8.35) for MDI; and 1.28 (95%CI: 0.90 to 1.83) ($p=0.004$ for interaction) for trials offering a choice between the two. Mortality associated with five deaths attributed to DKA, and two sudden deaths, was significantly increased ($p=0.007$) whereas mortality due to macrovascular causes was not significantly ($p=0.16$) decreased (three vs eight deaths for intensive vs conventional treatment).

18.1.5 Summary

The DCCT and EDIC clearly demonstrated that intensive glycaemic control in adolescents and adults with type 1 diabetes reduced the risk of onset or progression of microvascular complications and development of macrovascular disease. The potential benefit of intensive glycaemic control needs to be individualised. Specifically, the benefit of intensive glycaemic control needs to be weighed against the risk of severe hypoglycaemia, in particular in young children, elderly patients, those with major comorbidities, and patients with autonomic neuropathy. In each of these cases, increased risk of severe hypoglycaemia and complications developing may necessitate modification of glycaemic targets set and the use of strategies to achieve the targets safely. People with end-stage diabetes complications, such as end-stage renal failure, heart failure or extensive cardiovascular disease, were not enrolled in the DCCT; therefore people with these complications may not benefit to the same degree from intensive glycaemic control as those who were studied in the DCCT.

Evidence statements	
Q18.1	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of microvascular outcomes. Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of cardiovascular disease.
Recommendation	
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).

Practice points	
PP18.1.1	Intensive glycaemic control refers to an implemented strategy of intensive glycaemic management and is only achieved by a 'package' of methods, including MDI or CSII, frequent insulin dose adjustment, blood glucose level monitoring at least four times per day, weekly measurement of 3am blood glucose levels, formal diabetes education, medical nutrition therapy and physical activity advice.
PP18.1.2	The generalisability of implementing an intensive glycaemic control strategy may be limited by the strict inclusion criteria in the clinical trials undertaken. The potential benefit of a strategy of intensive glycaemic control needs to be individualised as much as is practical.
PP18.1.3	Observational data from the DCCT suggest that the greatest absolute benefit from an intensive management approach will be seen in those with higher HbA _{1c} levels if such improved HbA _{1c} levels can be achieved and sustained.
PP18.1.4	Transient worsening of some diabetes complications, particularly diabetic retinopathy, can occur some months after commencement of intensive glycaemic management, and clinicians should monitor for and manage these complications. Ophthalmologic monitoring before initiation of intensive treatment and at 3-month intervals for 6–12 months thereafter seems appropriate for such patients. In patients whose retinopathy is already approaching the high-risk stage, it may be prudent to delay the initiation of intensive treatment until photocoagulation can be completed, particularly if the HbA _{1c} is high.
PP18.1.5	A strategy of intensive glycaemic control maintained for some 6–7 years leads to persistent microvascular benefits and new macrovascular benefits 10 years later (so-called 'metabolic memory'); this emphasises the importance of tight glycaemic control relatively early in the disease course to achieve sustained outcomes in minimising long-term complications of diabetes.
PP18.1.6	While intensive glycaemic control to reduce long-term end-organ diabetes complications is readily justified at a health economics level, it needs to be adequately resourced and appropriately targeted for the benefits observed in the RCTs to be achieved.
CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Complications and Control Trial; HbA _{1c} , glycated haemoglobin; MDI, multiple daily injection; RCT, randomised controlled trial	

18.1.6 Cost effectiveness

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative provides background information only; no evidence-based guidelines are referenced in this section.

Cost-effectiveness studies demonstrate that the annual cost of intensive treatment is approximately three times the cost of conventional treatment. Such studies indicate that a strategy of Intensive glycaemic control in people with type 1 diabetes with the characteristics of those included in the DCCT, is strongly justified to reduce the long-term complications of diabetes; the incremental cost per year of life gained by intensive treatment is US\$28 661. Through simulation and extrapolation of projected cumulative incidences by age 70 years, intensive treatment would prevent all stages of microvascular and macrovascular complications. In addition, the end-stage severe diabetes complications, including blindness, end-stage renal disease and lower extremity amputation, would be markedly reduced (by 50% or more). Total and cardiovascular mortality would also be reduced. Incorporating hypoglycaemia into the model was reported to have little or no effect on the results. Thus, over a lifetime, DCCT-defined intensive treatment would reduce complications, improve quality of life, and could be expected to increase length of life (Nathan et al 2005). Other studies using intensive treatment, including the Stockholm Diabetes Intervention Study (Reichard et al 1999), found similar cost effectiveness to the DCCT.

18.2 Effectiveness of antihypertensive agents at controlling blood pressure and reducing complications

Question 18.2

(i) How effective are antihypertensive agents at controlling blood pressure in type 1 diabetes?

(ii) How effective are antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?

The detailed systematic review of this question is in Chapter 18 of the accompanying technical report, and the evidence matrix is in Section C18 of Appendix C

18.2.1 Blood pressure control

Hypertension is a pathogenic factor in macrovascular and microvascular events in diabetes (Jandeleit-Dahm and Cooper 2002). Systemic hypertension occurs most commonly in type 1 diabetes as essential hypertension in the presence or absence of the metabolic syndrome and in the setting of diabetic nephropathy (Jandeleit-Dahm and Cooper 2002). The renin–angiotensin–aldosterone system has long been implicated in mediating adverse effects on diabetic nephropathy through systemic blood pressure-dependent and independent mechanisms (Jandeleit-Dahm and Cooper 2002).

Three RCTs met the inclusion criteria to examine the effectiveness of antihypertensive agents in type 1 diabetes (Parving et al 1989; Gerds et al 1998; Andersen et al 2000). The studies varied in duration from about 7–12 months, and examined ACEI or angiotensin receptor blocker (ARB) therapy in one study arm. Participants generally had some degree of diabetic nephropathy, and all had mild-to-moderate systemic hypertension. Casual clinic blood pressure readings or 24-hour ambulatory blood pressure were study endpoints. Some studies followed up-titration and treat-to-target protocols. The studies collectively indicated that antihypertensive therapy, with the introduction of a single agent, reduced systolic blood pressure by about 6–12 mmHg and diastolic blood pressure by about 5–9 mmHg. Mean 24-hour blood pressure readings in the study group were 5–9 mmHg lower than in the placebo group. When different agents were compared, there were no differences in blood pressure control. Overall, adverse events ascribed to the active therapy during the studies were reported to be few.

In summary, these short-term, small studies demonstrate that antihypertensive agents are effective in type 1 diabetes in lowering blood pressure, similar to the effects seen in the general population. ACEI and ARB therapy, which were studied in these clinical trials, are preferred first-line agents in adults with diabetes in international guidelines (National High Blood Pressure Education Program 2004). ACEI are recommended for use in children with hypertension; they have been effective and safe in children in short-term studies (Donaghue et al 2009). In all patients with elevated blood pressure, nonpharmacological strategies and ongoing motivation for adherence to antihypertensive therapies are necessary (National High Blood Pressure Education Program 2004). Recent data from Australia indicate that antihypertensive agents, mainly ACEI and ARBs, are commonly used in adults with type 1 diabetes (Department of Health and Ageing 2009).

In people with diabetic nephropathy, systemic hypertension is common, and multiple agents are often required to achieve blood pressure targets (Andros et al 2006). Recent discussion has focused on whether there should be one blood pressure target for most adults with type 1 diabetes, or whether factors such as calculated cardiovascular risk should also play a

role (Cooper-Dehoff et al 2011). At present, most guidelines recommend a blood pressure target of less than 130/80 mmHg, and in the presence of 1 g daily or more of proteinuria, less than 125/75 mmHg (National High Blood Pressure Education Program 2004). In children and adolescents, blood pressure targets are based on age, gender and height specific percentiles. Contemporary (International Society for Pediatric and Adolescent Diabetes) guidelines recommend a target blood pressure of <90th percentile by age, sex and height (Donaghue et al 2009).

18.2.2 Effectiveness of antihypertensive agents at reducing complications

The evidence base for this question was one Level I study of good quality and seven Level II studies, mostly of good quality.

The nephropathy studies were heterogeneous regarding study type and their baseline population proteinuria status. The ACEI in Diabetic Nephropathy Trialists Group meta-analysis included 12 Level II studies, involving 698 microalbuminuric participants without hypertension, who were given active treatment for at least 1 year. The studies consistently observed beneficial treatment effects of ACEI (ACEI Trialist Group 2001). In patients receiving ACEI, progression to macroalbuminuria was reduced (OR 0.38, 95%CI: 0.25 to 0.57) and regression to normoalbuminuria was increased (3.07, 95%CI: 2.15 to 4.44). When the 2-year data were estimated, the albumin excretion rate was 54% lower in patients receiving ACEI than in those receiving placebo (95%CI: 37% to 66%). The magnitude of the effect on lowering albumin excretion was related to baseline levels: 74% for those whose baseline albumin excretion rates were at the upper boundary of microalbuminuria (200 ug/min), compared with 18% in those whose baseline microalbuminuria was at the lower boundary (20 ug/min) ($p=0.04$).

Primary prevention studies are the Diabetic Retinopathy Candesartan Trials (DIRECT) and RASS. One study (DIRECT-renal) examined the development of new onset microalbuminuria, in normotensive patients and found no effect with ARB (Bilous et al 2009). In the RASS study, there was no reduction in new onset of microalbuminuria with ACEI (Mauer et al 2009).

An earlier study by Lewis et al (1993) was in a proteinuric population; thus, the measurement of disease progression differed from the other studies as the degree of nephropathy at study enrolment was more advanced. The ACEI, captopril, significantly reduced the time to doubling of serum creatinine ($p<0.007$), with a 48% risk reduction in the captopril group compared with placebo; and significantly reduced combined death or dialysis and transplantation ($p<0.006$). An aggregate analysis over the 4 years of the study revealed significantly less proteinuria in the captopril group ($p=0.001$). The efficacy was better than that achieved by blood pressure control alone in the placebo group. The generalisability of the body of evidence is limited by the inclusion of only adults in all trials. Although the baseline hypertensive status of populations varied between trials, as did the proteinuric state, benefit was seen across all stages of diabetic nephropathy examined. Regarding applicability, populations were drawn from multiple study sites in multiple countries, including America, Australia, Europe and New Zealand.

The body of evidence for retinopathy as an outcome consisted of three large Level II studies addressing prevention of retinopathy onset and progression. Two of these studies were of good quality: DIRECT-Prevent/DIRECT-Protect (Chaturvedi et al 2008) and RASS (Mauer et al 2009); the third – EUCLID – was of fair quality (Chaturvedi et al 1998). EUCLID examined normotensive patients, but did not assess new retinopathy as a primary outcome. Only one study examined incidence of retinopathy: in the DIRECT-prevent study, patients treated with ARBs had reduced incidence of retinopathy onset (hazard ratio for candesartan vs placebo

0.82, 95%CI: 0.67 to 1.00, p=0.05). The studies were conflicting in relation to progression of retinopathy; the DIRECT-protect study showed no effect (Chaturvedi et al 2008), the RASS study showed a reduction for ACEI (OR 0.35) and ARB (OR 0.3), and the EUCLID study showed a significant reduction in the progression of retinopathy, using a completers analysis method rather than intention to treat. In EUCLID, after 2 years of treatment with lisinopril, the progression of diabetic retinopathy by one level was reduced by 50% (95%CI: 28% to 89%, p=0.02). Progression to proliferative diabetic retinopathy was reduced in the lisinopril group by 82% (OR 0.18, 95%CI: 0.04 to 0.82, p=0.03). The authors concluded that the EUCLID findings would need to be confirmed before changes to clinical practice could be advocated. The generalisability was limited, because only adults were studied. Patients were normotensive and varied by baseline retinopathy status. These studies were multicentre and included populations from America, Europe and the United Kingdom.

For cardiac autonomic neuropathy, the body of evidence consisted of two small, short-term Level II studies of poor and good quality (Ebbehøj et al 2002; Lanza et al 2007). The risk of bias was high. The studies were consistent in showing a statistically significant improvement in various aspects of cardiac autonomic neuropathy measurement. However, apart from reduced heart rate variability and an increase in RR interval in both studies, measurements showing improvement differed between studies and therefore cannot be compared. As neither study examined clinical endpoints, the clinical impact of these studies is small. The small size and short-term nature of the studies limit their generalisability. Both studies were conducted at single sites in Europe. Studies of antihypertensive therapy in peripheral neuropathy were not identified.

Overall, there is evidence that ACEI prevent progression of pre-existing nephropathy. Evidence of their effect on the onset of nephropathy or retinopathy is lacking, and evidence on prevention of progression of retinopathy or autonomic neuropathy is inconclusive or limited.

Evidence statements	
Q18.2	<p>Level II evidence shows that antihypertensive agents are effective at lowering blood pressure.</p> <p>NEPHROPATHY</p> <p>Primary prevention: In normotensive normoalbuminuric patients with type 1 diabetes, there is consistent evidence that neither ACEI nor ARB prevent the onset of microalbuminuria.</p> <p>Secondary prevention (progression): There is evidence that the use of ACEI prevents the progression from microalbuminuria to macroalbuminuria.</p> <p>There is evidence that ACEI attenuates or delays the progression from macroalbuminuria to doubling of creatinine or end-stage renal disease (combined death, dialysis and transplantation).</p> <p>RETINOPATHY</p> <p>Primary prevention: In normotensive patients with type 1 diabetes and no retinopathy, there is insufficient evidence to determine the effect of ACEI or ARB on the onset of retinopathy.</p> <p>Secondary prevention: In normotensive patients with type 1 diabetes and nonproliferative diabetic retinopathy, ACEI or ARB reduce the progression of retinopathy.</p> <p>Prespecified outcomes were two grades of retinopathy progression on the ETDRS scale (DIRECT and RASS) or one grade (EUCLID), thus with differing study outcome measures.</p>
Recommendation	
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B).

Practice points	
PP18.2.1	For patients who are intolerant of ACEI, ARBs can be used as an alternative treatment for the secondary prevention of nephropathy.
PP18.2.2	On the basis of the systematic evidence, including data in adolescents(Cook et al 1990), ACEI in type 1 diabetes can control albuminuria in normotensive microalbuminuria; however, there are currently restrictions from the Therapeutic Goods Administration to be considered in their use in this setting of normotension.
PP18.2.3	Tight control of blood pressure is of critical importance in limiting the progression of retinopathy and nephropathy. The general blood pressure target is <130/80 mmHg and <125/75 mmHg in the presence of 1 g daily or more of proteinuria.
PP18.2.4	ACEI and ARBs are contraindicated in pregnancy.
PP18.2.5	A small study has raised concerns that oral contraceptive use in women with type 1 diabetes may limit the efficacy of ACEI and ARB and contribute to macroalbuminuria(Ahmed et al 2005). Large prospective studies are required to further investigate this relationship.
ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker	

18.3 Effectiveness of statin therapy in reducing complications

Question 18.3 (interventional)

What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

The detailed systematic review of this question is in Chapter 18 of the accompanying technical report, and the evidence matrix is in Section C18 of Appendix C

In type 1 diabetes, a diet that is low in saturated fat and high in fruit and vegetables, a healthy body weight and regular physical activity are crucial for reducing macrovascular risks. These factors constitute the usual lifestyle prescription to lower macrovascular risk. Such nonpharmacological treatment is routinely desirable in type 1 diabetes. Glycaemic control can improve some lipid levels, especially circulating high triglycerides and low HDL-cholesterol, in people with type 1 diabetes in whom HbA_{1c} levels are elevated (Perez et al 2000).

There is strong evidence for the effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors (termed *statins* as a class) in reducing total and low-density lipoprotein (LDL) cholesterol and cardiovascular events in people with type 2 diabetes, whether or not they have macrovascular disease (Marshall et al 2004). However, cardiovascular endpoint studies involving statin administration in type 1 diabetes have been more limited.

In terms of vascular outcomes, the Cholesterol Treatment Trialists analysed the data from 18 686 individuals with diabetes from a previously published prospective meta-analysis of statins on CHD and other major vascular events (CTT Collaborators 2008). The aim of this large, fair-quality meta-analysis was to examine effects of statins on major coronary and major vascular events in patients with diabetes. Studies included in the meta-analysis were those that had an intervention that modified lipid levels, and that aimed to recruit 1000 or more participants, with treatment duration of at least 2 years.

Of the 14 studies in the meta-analysis, 11 provided data on middle-aged to older adult patients with type 1 diabetes. Trial participants were considered to have diabetes if they had a recorded history of diabetes at randomisation. Subdivision of diabetes type was based on the definitions used in the individual trials. Of 90 056 participants, 18 686 (20%) had

diabetes. Further subdivision showed that 1 466 (1.6% of the 20%) of these participants had type 1 diabetes. Baseline characteristics of patients presenting with type 1 diabetes included a mean age of 55.1 years, 21% smokers and 56% with a history of any vascular disease (previous heart attack or CHD, stroke or peripheral arterial disease). The mean blood pressure was 140/78 mmHg. The mean total cholesterol was 5.7 mmol/L, LDL-cholesterol 3.4 mmol/L, and HDL-cholesterol 1.3 mmol/L.

The percentage of participants with type 1 diabetes was small in the original trials, which may have increased the risk of allocation bias. The interventions studied included simvastatin 20–40 mg, pravastatin 40 mg, lovastatin 40–80 mg, fluvastatin 40–80 mg and atorvastatin 10 mg. In participants with type 1 diabetes, the mean (standard error) differences in plasma lipid concentrations at 1 year in participants exposed to statins and controls were as follows:

- total cholesterol –1.04 mmol/L (0.08)
- LDL -cholesterol –0.96 mmol/L (0.15)
- triglycerides –0.09 mmol/L (0.08).

There was no change in HDL—cholesterol levels. Regarding adverse events, there were too few cases of rhabdomyolysis reported in patients with diabetes for meaningful analysis.

Results indicated that there was some evidence of benefit in the 1466 people with type 1 diabetes (RR 0.79, 99%CI: 0.62 to 1.01, $p=0.01$) in terms of proportional reduction per mmol/L LDL cholesterol. Also reported was a reduction in the incidence of major vascular events by about 20% per mmol/L LDL-cholesterol reduction in all prognostic subgroups of participants with diabetes that were examined. After 5 years of treatment, 42 fewer patients per thousand had a vascular events per mmol/L cholesterol reduction. This benefit was greater for those with a history of vascular disease (57 per 1000) than those without (36 per 1000).

The remaining nine Level II studies were consistent in reporting a statistically significant reduction in total cholesterol and LDL-cholesterol with statin use in adults. The order of magnitude of statistically significant difference in total cholesterol ranged from –1.2 to –2.1 mmol/L treatment (compared to placebo) at the end of each study. The percentage reduction in total cholesterol from baseline to end of treatment in the statin groups ranged from –21% to –33%. Regarding LDL-cholesterol, the magnitude of difference ranged from –0.85 to –1.7 mmol/L treatment compared to placebo. In terms of percentage reduction in the treatment groups from baseline to study end, the range was –29 to –48%. Five studies showed a nonsignificant effect of statins on triglyceride levels (Hommel et al 1992; Kjaer et al 1992; Zhang et al 1995; Mullen et al 2000; Fried et al 2001). Two studies (Rustemeijer et al 1997; Noutsou and Georgopoulos 1999) reported a significant reduction in triglycerides and one (de Vries et al 2005) showed a significant reduction in triglycerides with doses of 20–40 mg but not 10 mg simvastatin. A statistically significant increase in HDL with statins was also reported (de Vries et al 2005) with all doses of simvastatin. One study (Manuel et al 2003) also showed a significant improvement in LDL-cholesterol, but this was not replicated in any of the other studies.

Overall, in type 1 diabetes, the evidence indicates a consistent biological effect of statins on circulating lipids, as seen in the general population. A meta-analysis of subgroup data showed that cardiovascular risk was also attenuated with statin use in type 1 diabetes. Studies underway, such as the Adolescent type 1 Diabetes Cardio-renal Intervention Trial

(AddIT), may provide further definitive evidence for the future use of statins in young adults and children (AddIT Research Group 2009).

Evidence statement	
Q18.3	Level I and II evidence demonstrates that statins are effective at reducing total and LDL cholesterol in adults with type 1 diabetes. Level I evidence demonstrates that statins reduce cardiovascular events in adults with type 1 diabetes.
Recommendation	
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).
Practice points	
PP18.3.1	As global macrovascular risk in type 1 diabetes is high in adults, statins should be commenced early in the disease course and before the development of cardiovascular disease.
PP18.3.2	Statin therapy can be used after Tanner stage II in boys and after menarche in females. In high-risk vascular disease states (e.g. hereditary LDL receptor deficiency), statins may be indicated from the age of 8 years.
PP18.3.3	Statin therapy is contraindicated in pregnancy, and reliable contraceptive methods should be used in females of reproductive age who are on statin treatment.
PP18.3.4	The benefit of statin therapy in people with end-stage renal failure (including in those with type 1 diabetes) has not been confirmed; however, it is prudent to use low-dose statin treatment in this group, which is at particularly high risk of cardiovascular disease.
LDL, low-density lipoprotein	

18.4 Cost and cost effectiveness of antihypertensive agents and statins

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative provides background information only; no evidence based guidelines are referenced in this section.

One review was identified that examined cost effectiveness of ACEI in patients with type 1 diabetes (Swislocki and Siegel 2001). The review included four studies and concluded that treatment of hypertensive patients with type 1 diabetes is cost effective. An Australian study used Markov modelling to compare intensive management with usual care for patients with suboptimally managed type 1 and type 2 diabetes and hypertension (Howard et al 2010). This study found that treating all known patients with diabetes with ACEI was both less costly (an average lifetime saving of \$A825 per patient) and more effective than current treatment (resulting in 0.124 additional quality-adjusted life years [QALYs] per patient). Several studies limited to patients with type 2 diabetes have demonstrated cost effectiveness for antihypertensive therapy. Intensive blood pressure control in hypertensive patients with type 2 diabetes reduced costs and improved health outcomes relative to moderate hypertension control (CDC Diabetes Cost-effectiveness Group 2002). Similarly, Markov modelling demonstrated that a hypertension management program in patients with type 2 diabetes was cost effective, and achieved greater gains in QALYs compared with standard care (Ly et al 2009).

A systematic review of cost effectiveness of interventions to prevent and control diabetes, which included 56 studies, found evidence that antihypertensive agents, and statin therapy (for the secondary prevention of cardiovascular disease), were cost saving and cost effective in type 2 diabetes (Li et al 2010). None of the included studies examined these therapies in patients with type 1 diabetes. ACEI therapy for intensive hypertension control compared

with standard hypertension control; ACEI or ARB therapy to prevent end-stage renal disease compared with no ACEI or ARB treatment; and early irbesartan therapy (at the microalbuminuria stage) to prevent end-stage renal disease compared with later treatment (at the macroalbuminuria stage) were all cost saving in type 1 diabetes.

18.5 Predictive ability of the Framingham multiple cardiovascular disease risk factor equation in type 1 diabetes?

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative provides background information only for health professionals; no evidence-based guidelines are referenced in this section. There are no predictive risk factor equations for type 1 diabetes; however, the prediction of cardiovascular risk in type 1 diabetes is discussed below.

In the course of a lifetime, many people with type 1 diabetes will develop clinically significant CHD (Sibal et al 2006). Risk factor algorithms have been developed, from long-term prospective cohort studies, to assess absolute risk of CHD and mortality. For the general population, the most widely used models for a first CHD event have been based on data from the Framingham Heart Study (Wilson et al 1987; Poole et al 2009). Some risk factor score methods, including the Framingham and the UKPDS Risk Factor Engine, have been validated in populations with type 2 diabetes (Stevens et al 2001; Nuevo et al 2009; van der Heijden et al 2009); however, they have not been shown to perform well in populations with type 1 diabetes (Zgibor et al 2006).

Two important issues for coronary heart disease (CHD) in type 1 diabetes are as follows (Sibal et al 2006):

- CHD events often occur earlier in life in type 1 diabetes than for people with type 2 diabetes or in the general community (due to the often earlier age onset of type 1 diabetes)
- Diabetic nephropathy as albuminuria or proteinuria, or reduced GFR, are common and major factors that contribute to CHD events that occur in type 1 diabetes.

In the EDIC study, the average age of onset of CHD events was 39 years (interquartile range 34–44 years), and renal disease was thought to contribute to about half of the CHD events that occurred (Nathan et al 2005). In contrast, in the general population, the age of onset of CHD events is the late 60s and early 70s (Carney et al 2009). The risk factor engines have not been designed for people in the 20 to mid-40s age group and do not include renal disease parameters. It is therefore not surprising that the risk factor engines performed poorly in predicting CHD events in people with type 1 diabetes (Zgibor et al 2006). Each risk factor engine markedly underestimated risk of first CHD events in people with type 1 diabetes.

Currently, there are no risk factor engines for CHD events in type 1 diabetes. Such tools would be desirable to help identify individuals at highest event risk. If developed from populations with type 1 diabetes, they are likely to include parameters of diabetes duration and renal status (estimated GFR and albuminuria status), as well as those of age, blood pressure and lipid status (Sibal et al 2006).

18.6 Frequency of screening for complications

This section was not systematically reviewed and as such, no recommendations or practice points are made. The narrative contains information from contemporary evidence based guidelines developed by the Australian Diabetes Society (Australian Diabetes Society 2008),

approved by the NHMRC in 2008, the International Society for Paediatric and Adolescent Diabetes (ISPAD) (Donaghue et al 2009) and the American Diabetes Association (ADA) (American Diabetes Association 2010). The grading of evidence used in the ADA and ISPAD guidelines is shown in Chapter 2, Section 2.2.3 (Table 2.2).

Subsequent to the diagnosis of diabetes, most people with type 1 diabetes will develop some microvascular end-organ complications in their lifetime (Roy et al 2004; Melendez-Ramirez et al 2010). Some people will also develop clinically significant and more severe progressive complications, such as vision-threatening retinopathy, diabetic nephropathy, or painful or insensate peripheral neuropathy (Roy et al 2004; Nathan et al 2005). As the decades progress, many people will also develop cardiovascular disease (CVD) – as coronary heart disease (CHD), cerebrovascular or peripheral arterial disease – with a CVD mortality rate in this group of approximately 40% (Secrest et al 2010b). However, recent studies have reported that frequencies of severe complications in patients with type 1 diabetes are lower compared with those reported historically, especially when the disease is treated intensively (Hovind et al 2003; Nathan et al 2005).

18.6.1 Mortality rates

Diabetes-related complications account for the excess deaths reported in people with type 1 diabetes. Nevertheless, mortality trends over recent decades in international prospective studies indicate that both men and women with type 1 diabetes are, on average, living longer than in the past (Nishmura et al 2001; Secrest et al 2010a). This improvement is consistent with:

- in the 1980s, increased use of HbA_{1c} testing and home blood glucose monitoring, along with potential improvements in glycaemic control, as well as improved blood pressure therapy
- in the 1990s, increased use of lipid-lowering therapy and further reductions in cigarette smoking.

However, compared with the general population, much higher mortality rates (13-fold for women and fivefold for men), continue to be reported in cohorts with type 1 diabetes (Secrest et al 2010a). This suggests a continuing major excess in mortality, ascribed mainly to renal and CVD (Secrest et al 2010b). In Australia, death rates in people with insulin-treated diabetes, which includes those with type 1 diabetes, remain three-fold higher than the general population (Australian Institute of Health and Welfare 2009). The cause of death in long-term prospective series of people with type 1 diabetes varies with diabetes duration and age. In one study of childhood-onset type 1 diabetes, in the first 10 years after diagnosis, the leading cause of death was acute diabetes complications (74%), while during the subsequent 10 years, deaths were evenly attributed to acute (15%), cardiovascular (22%), renal (20%) or infectious (18%) causes. After 20 years of diabetes, chronic diabetes complications (cardiovascular, renal or infectious) accounted for more than 70% of all deaths (Secrest et al 2010b).

In addition to the presence of diabetes complications, other factors that predict mortality are higher waist:hip ratio, and elevated levels of cholesterol other than high-density lipoprotein (HDL) cholesterol (Soedamah-Muthu et al 2008). In contrast, longevity in type 1 diabetes is predicted by higher HDL cholesterol levels and more normal body habitus or body mass index (Bain et al 2003).

18.6.2 Value of screening

The value of screening for chronic diabetes organ complications is that:

- detecting early complication changes may help to better identify those who may benefit from intensive control of blood glucose and early targeting of other surrogate vascular risk factors (e.g. blood pressure) (Marcovecchio and Chiarelli 2010)
- additional interventions have been shown to help prevent end-stage complications.

These interventions include laser photocoagulation therapy for proliferative diabetic retinopathy or macular oedema, angiotensin converting enzyme inhibitor (ACEI) therapy for diabetic nephropathy, and preventive foot care for people with peripheral neuropathy (Melendez-Ramirez et al 2010). Normoalbuminuric people with type 1 diabetes have a mortality risk over subsequent decades that is similar to the general population without diabetes, emphasising the importance of preventing diabetic nephropathy (Orchard et al 2010).

18.6.3 Screening methods

Consensus guidelines indicate that adults with type 1 diabetes should undergo microvascular screening for diabetic retinopathy, nephropathy and peripheral neuropathy, using standard methods, on an annual basis, from 5 years after the diagnosis of their diabetes (Canadian Diabetes Association 2008; 2011). These methods include fundoscopy and visual acuity; albuminuria (spot albumin to creatinine ratio or timed urine collection for albumin excretion rate) and determination of estimated glomerular filtration rate (GFR); and assessment of ankle reflexes, feet vibration perception, and ability to detect the 10 g 5.07-gauge Semmes-Weinstein monofilament (Canadian Diabetes Association 2008). Australian research has indicated that early evidence of microvascular complications of diabetes (background retinopathy prevalence of 12%) are found when diabetes onset occurs in childhood and adolescence, and nonproliferative diabetic retinopathy can occur within 2 years of diagnosis in type 1 diabetes (Cho et al 2010). Retinopathy screening for diabetes that has had its onset in childhood and adolescence is recommended two years after diabetes diagnosis (for pubertal-onset type 1 diabetes), and after five years (or after age nine years,) for prepubertal onset diabetes (APEG 1996; Donaghue et al 2009).

18.6.4 Current recommendations for screening

In general, Australian and international consensus recommendations indicate that, once screening for microvascular complications has started in type 1 diabetes, it should then occur yearly for diabetic nephropathy and every 1–2 years for retinopathy (Australian Diabetes Society 2008; Hanas et al 2009; American Diabetes Association 2010), see Table 18.1. In lower risk cases, the frequency of subsequent screening for diabetic retinopathy could be reduced from once a year to once every two years on the advice of an experienced eye care professional (Donaghue et al 2009; American Diabetes Association 2010).

There are no agreed universal recommendations for screening macrovascular disease in people with type 1 diabetes, other than in adults, where screening involves undertaking a thorough history and performing a detailed examination annually, and possibly a resting electrocardiogram (ECG) yearly or every 2 years (Canadian Diabetes Association 2008; American Diabetes Association 2010). The clinical assessment includes taking a history for new onset symptoms of ischaemic heart disease, including typical or atypical chest pain or unexplained dyspnoea on exertion, and examining for carotid bruits and lower limb pulses (Canadian Diabetes Association 2008). The American Diabetes Association indicates that, in people with type 1 or type 2 diabetes, candidates for cardiac stress testing include those

with typical or atypical cardiac symptoms, or an abnormal resting ECG (American Diabetes Association 2010). The Canadian Diabetes Association includes as candidates for testing those with known cerebrovascular or peripheral arterial disease (Canadian Diabetes Association 2008). Dynamic screening investigations to be considered for CVD include stress echocardiography or nuclear medicine (SestaMIBI) heart study, depending on local expertise (Canadian Diabetes Association 2008). Therefore, certain less traditional risk factors should be considered to help stratify risks and identify people who may need screening for cardiovascular complications of diabetes, in addition to the conventional risk factors of severe hypertension, dyslipidaemia or smoking. These additional risk factors include diabetes duration (>15 years), a first-degree family history of premature cardiovascular disease, presence of active diabetic retinopathy, and occupations with a relatively high risk (e.g. occupations that involve driving a commercial motor vehicle regularly) (Canadian Diabetes Association 2008).

Table 18.1 – Suggested frequency of screening for complications in type 1 diabetes

	When to commence screening	Frequency	Method of screening
Retinopathy	After 2yrs duration in adolescents and adults, after 5yrs duration and from age 9yrs in children	2nd yearly Annually (high risk, long duration, high A1c, NPB retinopathy)	Slit lamp biomicroscopy Retinal photography Mydriatic funduscopy Visual acuity
Nephropathy	After 2 yrs in adolescents and adults, after 5 yrs duration and from age 9yrs in children	Annually	Timed albumin excretion rate First morning albumin creatinine ratio Spot urinary albumin to creatinine ratio
Neuropathy	Annually	Annually	Physical examination Monofilament Vibration & thermal threshold Autonomic nerve tests
Lipids	At diagnosis if family history or from 12yrs of age	Every 5 years until puberty, then annually	Fasting cholesterol, LDL cholesterol
Blood pressure	At diagnosis	At least annually	Sphygmomanometer 24 hour BP measurements
Macrovascular disease	In adulthood	At least annually	Clinical assessment and consider resting ECG

18.6.5 Emerging screening technologies

The development of new sensitive methods to detect more subtle, subclinical diabetes complications in people with shorter duration type 1 diabetes is an area of ongoing intensive clinical research (Marcovecchio et al 2010). To date, noninvasive approaches (including in children) of corneal confocal microscopy to detect early structural tissue changes of diabetic neuropathy, vascular and B mode ultrasound to examine blood vessel and cardiac function, and pupillometry to screen for autonomic neuropathy (Cho et al 2010). Standard field retinal fundus photography analysing retinal vascular dilatation (Cheung et al 2008) and branching (Cheung et al 2009a) can predict impending classical diabetic retinopathy. In one study,

cystatin C levels detected early abnormalities of glomerular filtration (Premaratne et al 2008). Other studies also estimate that up to half of the susceptibility to microvascular complications of diabetes is due to common genetic polymorphisms (Wiltshire et al 2008; Barrett et al 2009; Wang et al 2010). It is envisaged that these technologies to better define microvascular complication risk and early change will continue to be developed, and that some will become routine screening approaches for detecting early microvascular pathology.

18.6.6 Individualised follow-up

Once a diabetes complication has developed, follow-up should be individualised to treat and monitor the complication. This will usually involve more frequent examinations of the complication after specific therapies have been started, and possibly also intensified general risk-factor management of blood glucose, blood pressure and lipids, and possibly antiplatelet therapy (Canadian Diabetes Association 2008). The safety of intensive glucose control has not been established in people with symptomatic CHD. Therefore, it may not be appropriate to intensify blood glucose control to minimise the risk of severe hypoglycaemia and precipitant cardiac events. In addition, in people with more severe end-stage complications (e.g. chronic kidney disease stages 3–5, or dense insensate peripheral neuropathy), there is no evidence that intensified blood glucose control will improve outcomes; glycaemic targets should therefore be individualised for each patient, taking into account the burden and severity of comorbidities (Canadian Diabetes Association 2008). In people with diabetes and CHD, revascularisation in the form of coronary stenting may help to relieve symptoms of CHD, and revascularisation in the form of coronary artery by-pass may also be indicated for prognosis where triple vessel or left main coronary artery disease exist (Schwartz 2009).

18.6.7 Other complications

Other complications of type 1 diabetes have been described, in addition to the classical microvascular and macrovascular complications. Associated autoimmune clusters can occur, so screening for coeliac disease and autoimmune thyroid disease are addressed in Chapter 20. Addison's disease is rare but occurs with increased frequency in type 1 diabetes; testing should be performed as clinically indicated. Psychological conditions, impact on physical development and chronic cognitive effects are addressed in Chapter 4. These diabetes complications are not, at present, universally or routinely screened for, but may be detected at regular clinical review, or as part of clinical research protocols. Type 1 diabetes can also cause cheiroarthropathy with limited joint mobility (Kordonouri et al 2009), lipohypertrophy at insulin injection sites (Overland et al 2009a), Charcot's arthropathy (Armstrong et al 1997), diabetic mastopathy (Ely et al 2000), and subclinical pulmonary disease (Wheatley et al 2010). Diabetic cardiomyopathy (Suys et al 2004) and the rare but devastating condition 'dead in bed syndrome' (Tu et al 2010) are also well recognised. Autoimmune skin conditions that are more common in type 1 diabetes include necrobiosis lipoidica diabetorum, vitiligo and granuloma annulare (Edidin 1985). Finally, certain infections, such as localised cutaneous or mucosal infections, or systemic fungal and bacterial infections, may be exacerbated by poor glycaemic control (de Leon et al 2002) and are not uncommon. Diabetes may also affect mortality and morbidity outcomes from sepsis (Yende and van der Poll 2009). A specific type of life-threatening fungal infection in type 1 diabetes is mucormycosis, which is more common in children (Simmons et al 2005). Increased periodontal disease prevalence is also reported and may lead to improvement in glycaemic control when treated (Simpson et al 2010).

19 Foot ulcers and Charcot's arthropathy

19.1 Introduction

National evidence-based guidelines for the prevention, identification and management of foot complications in type 2 diabetes were approved by the NHMRC in 2011 (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011). The guidelines inform clinicians of best practice for preventing, identifying and managing foot disease in adults with type 1 or 2 diabetes, in both urban and rural or remote primary care, and in specialist foot centres. The guidelines are equally relevant for type 1 diabetes. In view of the availability of these contemporary guidelines, this chapter was not systematically reviewed. The reader should refer to these guidelines for further information.

19.2 Foot complications in young people with type 1 diabetes

Children and adolescents with type 1 diabetes usually do not display the severe foot problems observed in older people with diabetes. Nevertheless, young people are at greater risk than their peers without diabetes of structural and functional foot abnormalities (Barnett et al 1995). In a prospective study of young people with type 1 and type 2 diabetes, most of the foot problems observed were potentially modifiable disorders of the skin and nails (69%), while a significant proportion (31%) were structural musculoskeletal disorders requiring referral to a podiatrist or orthotist (Rasli and Zacharin 2008).

Foot abnormalities not specific to diabetes – including deformity, plantar callus and high plantar pressure – may contribute to soft-tissue breakdown and ulceration. Structural changes that are specific to diabetes – including soft-tissue thickening and limited joint mobility in the foot – may alter the mechanics of the foot, leading to high plantar pressure and ulceration. Functional abnormalities (see Box 19.1, below) can result in abnormal pressure changes on the plantar surface of the foot, or abnormal pressure from footwear (AIHW 2008).

Box 19.1 Paediatric foot abnormalities that may lead to abnormal plantar pressure

- Significant leg length discrepancy (>1 cm).
- Genu varum (normal up to the age of 2 years) or genu valgum (normal between 2 and 7 years).
- Internal or external knee position.
- Varus or valgus foot position (a small degree of valgus alignment is normal up to 7 years).
- In-toeing or out-toeing.
- Abnormal shoe wear patterns – the heel should wear to the centre or slightly laterally; the sole should show even wear; and the upper of the shoe should not be deformed.
- Inadequate shoe fit – either too small or too large.

Plantar callus and increased plantar pressure have been observed more commonly in young people with type 1 diabetes (Duffin et al 2003). Plantar callus can increase plantar pressure, which may damage underlying soft tissue; in adults with diabetes, this is a reliable predictor of subsequent ulceration (Murray et al 1996). Plantar pressure is evaluated by using pressure analysis equipment, which is available at most high-risk foot clinics and diabetes complications assessment clinics.

Thickening of the plantar aponeurosis – which indicates loss of elasticity and thickening of the dermis, and is a marker of tissue collagen glycation and oxidation – has been observed in one-third of young people with type 1 diabetes (Duffin et al 2002). Thickening of the plantar aponeurosis was associated with increased forefoot plantar pressure and limited joint mobility in a study of adults with type 1 and 2 diabetes (D'Ambrogi et al 2003), and with limited subtalar joint mobility in young people with type 1 diabetes (Duffin et al 2002). Thickening of the plantar fascia is also a risk factor for subsequent development of microvascular complications, including peripheral neuropathy (Craig et al 2008).

Limited joint mobility has also been detected in the feet of young people with diabetes (Barnett et al 1995; Duffin et al 2002), affecting the ankle, subtalar, first metatarsophalangeal and interphalangeal joints. Joint limitation in the first metatarsophalangeal joints increases plantar pressure under the hallux, an area at great risk of developing a plantar ulcer (Duffin et al 2003). Limited joint mobility increases plantar pressure, which in turn may lead to tissue breakdown and ulceration, although this is rarely observed in young people with diabetes. Limited joint mobility at the first metatarsophalangeal joint is indicated by dorsiflexion (in a weight-bearing position) of less than 60 degrees, and warrants further assessment.

19.3 Foot complications in adults with type 1 diabetes

The spectrum of diabetes-related complications that affect the foot in adults is different from that observed in young people. In adults, complications include ulceration, deformity, ischaemia, infection (including osteomyelitis) and Charcot's neuroarthropathy (CNA). The pathophysiology of foot ulceration is complex and multifactorial. Peripheral neuropathy, peripheral vascular disease, foot deformity, trauma, skin infection, impaired healing and limited self-care, may all contribute to foot ulceration or failure of ulcer healing. Failure of foot ulcers to heal can lead to foot amputation.

Peripheral neuropathy, foot deformity and external trauma are all common causes of foot ulceration in diabetes, together with peripheral vascular disease and peripheral oedema (Boulton 2008). In a population-based sample of Australian adults with diabetes aged 25 years or more (the Australian Diabetes, Obesity, and Lifestyle Study) (Tapp et al 2003), a substantial proportion (about 20%) were at risk of foot ulceration, which is a leading cause of hospitalisation for people with diabetes (AIHW 2008). Diabetes is the most common cause of nontraumatic lower limb amputation in Australia (Barr et al 2006). The 5-year survival for those who have had limb amputation is poor, with mortality rates ranging from 39% to 80% (Moulik et al 2003).

The risk of foot ulceration and amputation is increased in patients with previous foot ulceration or previous amputation, peripheral neuropathy, peripheral vascular disease and foot deformity (including hallux deformity, hammer or claw toe, callus, previous amputation, flattened arches, abnormally wide feet and CNA). Older age is a significant risk factor for diabetes-related foot complications; in addition, evidence suggests that visual impairment, kidney disease, poor glycaemic control, ill-fitting footwear and socioeconomic disadvantage

are also risk factors (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011).

CNA is a noninfectious, degenerative disease of the bones and joints, particularly weight-bearing joints such as the foot and ankle. The condition is characterised by joint dislocation, fractures and deformities. In extreme cases, it may significantly disrupt the bony architecture of the affected joint. In developed countries, CNA typically manifests most commonly in patients with long-standing diabetes and peripheral neuropathy. About half of people with CNA experience some pain, however the severity of the pain may be less than clinical signs and symptoms would seem to indicate. Specific clinical signs indicating the presence of CNA include unilateral swelling and joint deformity, an increase in local skin temperature (generally about 3°C higher in the affected extremity), erythema, joint effusion or oedema, absence of sweating, bounding pedal pulses, an insensate foot and bone resorption. Instability, loss of joint function and concomitant ulceration may also be evident.

Suspected CNA of the foot is considered an emergency and should prompt immediate referral to a dedicated multidisciplinary foot care service. Early management aims to eliminate further trauma or stress to the foot by preventing weight bearing, thus preventing progression of the disease. Offloading with a total contact cast – widely accepted as the most effective treatment for patients with CNA – protects the foot, and reduces foot temperature and bone activity. Complications that may arise from inadequate or delayed treatment include foot deformity, chronic ulceration, infection and osteomyelitis.

Prevention of foot complications in people with diabetes includes (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011):

- podiatry
- hygiene maintenance (advice to inspect and wash feet daily)
- appropriate footwear and hosiery
- protective shoes (avoid constrictive footwear)
- diabetes clinic contact initiated by the patient, if concerned (McCabe et al 1998).

19.4 Screening for foot complications in type 1 diabetes

This section examines methods for and frequency of screening for foot complications in children, adolescents and adults with type 1 diabetes. No studies have evaluated the effectiveness of screening for foot complications in children and adolescents. Similarly, no studies have addressed the optimal frequency of screening.

Screening for foot problems in adults is associated with a reduction in ulceration and reduction in major and total amputation. One large randomised controlled trial examined the effects of a two-stage foot-screening program followed by a foot-protection program for those classified as high risk for foot ulceration compared to standard care (Lemaster et al 2008). People classified as high risk were entered into a foot-protection program that included foot care (podiatry and hygiene maintenance), support hosiery and protective shoes. Those classified as low risk received no further special treatment. A significant reduction in major and total amputation was demonstrated in the intervention group, and there was a trend to increased ulcer healing. Nonrandomised, observational studies have demonstrated that other commonly used clinical assessments are effective in predicting foot ulceration or amputation.

Tools for assessing neuropathy, circulation and foot deformity are shown in Box 19.2 (Baker IDI Heart and Diabetes Institute et al 2011).

Box 19.2 Tools for assessing neuropathy, circulation and foot deformity

Neuropathy

- 10 g monofilament sensitivity.
- Vibration perception (biothesiometer).
- Neuropathy Disability Score – ankle (Achilles) reflexes and the sensory modalities of pinprick, light touch, vibration and temperature perception.

Circulation

- Palpation of peripheral pulses.
- Ankle-brachial index.

Foot deformity

Six-point scale (1 point for each characteristic):

- small muscle wasting
- Charcot foot deformity
- bony prominence,
- prominent metatarsal heads,
- hammer or claw toes
- limited joint mobility

Score of 3 or above indicates foot deformity

19.5 Summary

The following summary points are adapted from National evidence-based guidelines for the prevention, identification and management of foot complications in type 2 diabetes (Baker IDI Heart and Diabetes Institute et al 2011)

- Foot care education should be provided to all people with diabetes to assist with prevention of foot complications.
- Podiatry review is an important component of a foot-protection program. However, in settings where this is not possible, a suitably trained, alternative health-care worker may undertake a review of the feet.
- In people identified as having low-risk feet (where no risk factors or previous foot complications have been identified), foot examination should occur annually.
- In people identified as having intermediate-risk or high-risk feet (without current foot ulceration), foot examination should occur at least every 3–6 months.

- People identified as having intermediate-risk or high-risk feet should be offered a foot-protection program that includes foot education, podiatry review and appropriate footwear.
- People with plantar callus, high plantar pressures or limited joint mobility need to be monitored closely for foot complications.
- People with diabetes-related foot ulceration are best managed by a multidisciplinary foot-care team.
- Given the limited access to multidisciplinary foot-care teams, at a minimum, the following factors should always precipitate referral to such a team:
 - deep ulcers (probe to tendon, joint or bone)
 - ulcers not reducing in size after 4 weeks, despite appropriate treatment
 - the absence of foot pulses
 - ascending cellulitis
 - CNA
- If access to a multidisciplinary foot-care team is limited, foot ulceration or foot complications other than those listed above should be managed by a general practitioner, together with either a podiatrist or a wound-care nurse.
- Remote expert consultation with digital imaging should be made available to people with diabetic foot ulceration living in remote areas who are unable to attend a multidisciplinary foot-care team or service for management.

20 Other complications and associated conditions

Individuals with type 1 diabetes are at increased risk of detectable organ-specific autoantibodies (e.g. thyroid and adrenal), and the development of autoimmune diseases such as thyroid and coeliac disease. This chapter examines the evidence for screening for these two conditions in children, adolescents and adults with type 1 diabetes.

20.1 Coeliac disease

20.1.1 Epidemiology

Coeliac disease is more common in patients with type 1 diabetes than in the general population. Prevalence ranges from 0.8% to 6.4% in adults, and 0.6% to 16.4% in children with type 1 diabetes (Bruno et al 2003; Cerutti et al 2004; Kordonouri et al 2009). In Australia, the prevalence in children is about 5% (Pham et al 2010), with an incidence of 0.72 per 100 person years (Glastras et al 2005). In people with diabetes, coeliac disease commonly presents as a silent disease, with few if any symptoms (Larsson et al 2008). Established risk factors include younger age at diagnosis of type 1 diabetes (Cerutti et al 2004), shorter duration of diabetes (Larsson et al 2008) and human leukocyte antigen (HLA) DQ2 (Doolan et al 2005). Younger children (aged <5 years) are more likely to be diagnosed with coeliac disease after longer diabetes duration compared with older children and adolescents, and are more likely to seroconvert after being negative on screening at diabetes diagnosis (Pham et al 2010).

Complications of seropositivity to coeliac antigens in children with type 1 diabetes include adverse effects on bone mineral density, weight standard deviation scores (SDS) (Artz et al 2008), body mass index (BMI) (Simmons et al 2007) and growth (Kaspers et al 2004). There are no data regarding these outcomes in the adult population.

20.1.2 Screening

Antibody screening tests for coeliac disease include those for antigliadin antibodies (AGA), either IgA or IgG; antireticulin antibodies (ARA), IgA; antiendomysium antibodies (EMA), IgA; and anti-tissue transglutaminase (tTGA and tTGG). These tests can give a false-negative result in IgA-deficient populations; therefore, a measure of total IgA is recommended at the time of screening.

Recommendations regarding screening for coeliac disease in patients with type 1 diabetes are not consistent. There are currently two issues; the type of screening tests to use and the timing of testing including frequency. The National Institute of Health and Clinical Excellence (NICE) guidelines recommend using tTGA as the initial test; IgA EMA if the result of the tTGA test is equivocal; IgA deficiency if serology is negative; and IgG tTGA or IgG EMA (or both) for people with confirmed IgA deficiency (NICE 2009). This guidance is based on a report from the Agency for Healthcare Research and Quality (AHRQ), which concluded that the IgA tTGA and IgA EMA tests show higher levels of sensitivity and specificity than the AGA tests. Inclusion criteria for all study participants, including controls, included a reference test of small bowel biopsy. The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend screening for IgA deficiency (which is present in 1:500 people) when

screening for coeliac disease by measuring the total IgA level, since tTGA antibodies may not be detected in IgA deficiency, resulting in a false negative test (Kordonouri et al 2009).

In regards to timing of screening, the ISPAD guidelines (Kordonouri et al 2009) advocate screening at diagnosis in all children with type 1 diabetes, with repeat annual screening for the first 5 years after diagnosis, and every 2 years thereafter. This is based on the reduced risk of coeliac disease with increasing diabetes duration. The guidelines do not stratify screening intervals by age.

In the presence of an elevated antibody level, a small bowel biopsy is required to confirm the diagnosis of coeliac disease by demonstrating subtotal villus atrophy, as outlined in the Marsh criteria (Marsh and Crowe 1995). To minimise false negative histology results, gluten exposure should not be restricted prior to the planned bowel biopsy.

20.1.3 Management

Following introduction of a gluten-free diet, mucosal changes reverse and antibody titres return to normal; however, there is insufficient evidence to demonstrate improvement in glycaemic control. The aims of treatment with a gluten-free diet are to reduce the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (osteoporosis, iron deficiency and growth failure). Patients with proven coeliac disease should be referred to a gastroenterologist, and receive education and support from an Accredited Practising Dietitian. Educational materials for patients and families should be made available.

Question 20.1

How and how often should patients with type 1 diabetes be screened for coeliac disease?

The detailed systematic review of this question is in Chapter 20 of the accompanying technical report, and the evidence matrix is in Section C20 of Appendix C

The systematic review identified seven longitudinal cohort studies (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Glastras et al 2005; Poulain et al 2007; Larsson et al 2008; Salardi et al 2008). Five of these were prospective studies, all of medium risk of bias, and two were retrospective, both of medium risk of bias. All of the studies were in children and adolescents (n=6506), with no prospective or retrospective, longitudinal studies found in adults. Thus, recommendations regarding frequency of screening could not be made for adults. The findings of the studies were consistent in demonstrating the high prevalence of antibodies for coeliac disease or biopsy-proven coeliac disease, mostly detected at the time of diagnosis of type 1 diabetes or within 2–4 years post diagnosis.

All studies were of fair quality, but only one included adults. The included studies demonstrated a high prevalence of antibodies for coeliac disease or of biopsy-proven coeliac disease in children and adolescents with type 1 diabetes and a decreasing trend in prevalence with duration of diabetes, with most cases being detected by screening at diagnosis of diabetes or up to 2–4 years post diagnosis (Barera et al 2002; Crone et al 2003; Cerutti et al 2004; Larsson et al 2008; Salardi et al 2008). Cerutti et al (2004) concluded from their data that coeliac disease is rarely found after 10 years duration of diabetes (Cerutti et al 2004). There are also some subgroups of patients for whom the risk of developing coeliac disease may be higher, with female sex and age of less than 4 years at diagnosis of type 1 diabetes being independently associated with the risk for having both coeliac disease and diabetes (Cerutti et al 2004). Additionally, positive antibodies at diagnosis are highly

predictive of future disease (Glastras et al 2005), suggesting the need for closer surveillance of patients falling into these subgroups.

The results therefore provide the rationale for routine screening at the time of diagnosis of type 1 diabetes and repeated at follow-up until the risk declines, although none of the studies were designed to address the optimal frequency of screening and none were undertaken in adults.

Evidence statements	
Q20.1	There is an increased risk of coeliac disease in children and adolescents with type 1 diabetes compared to general population historical rates. The number of new cases detected 1 and 2 years after diagnosis is similar to the number of cases at diagnosis. The number of new cases detected after 10 years of diabetes duration is similar to the general population.
Recommendation	
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).
Practice points	
PP20.1.1	Adults with newly diagnosed type 1 diabetes should be screened for coeliac disease at diagnosis.
PP20.1.2	Adults with type 1 diabetes who have not been previously screened should be screened for coeliac disease.
PP20.1.3	Children and adolescents should be rescreened for coeliac disease at least once in the first five years after diagnosis.

20.2 Thyroid disease

20.2.1 Epidemiology

Thyroid disease is the most common autoimmune disease in patients with type 1 diabetes; it occurs more commonly in children and adults than in the general population (Mantovani et al 2007; Volzke et al 2007; Somers et al 2009). At diagnosis of type 1 diabetes, 8–15% of young people have positive thyroid peroxidase (TPO) antibodies (Glastras et al 2005; Kordonouri et al 2005) and the cumulative incidence of thyroid autoimmunity ranges from 10% to 22% after up to 10 years of diabetes (Kordonouri et al 2005; Severinski et al 2009). Among 28 671 patients aged under 30 years with type 1 diabetes from Germany and Austria, thyroid autoimmunity was found in 20% (Warncke et al 2010). The prevalence of primary hypothyroidism ranges from 3% to 8% in young people (Hansen et al 2003; Severinski et al 2009). Hyperthyroidism is less common than hypothyroidism in association with type 1 diabetes (Umpierrez et al 2003), but is still more common than in the general population.

Among children and adolescents with type 1 diabetes, the prevalence of thyroid autoimmunity is associated with female gender, older age and longer diabetes duration (Kordonouri et al 2005; Karavanaki et al 2009; Severinski et al 2009; Warncke et al 2010). The risks of thyroid autoimmunity and thyroid disease are also higher in adult women (Perros et al 1995; Umpierrez et al 2003). The risk of developing thyroid disease (hypothyroidism or hyperthyroidism) is greater among those who have evidence of thyroid autoimmunity at diagnosis of type 1 diabetes (Umpierrez et al 2003; Glastras et al 2005; Kordonouri et al 2005), particularly if thyroid autoantibody titres are high (Kordonouri et al 2005).

20.2.2 Clinical features

Autoimmune thyroid disease may present as a subclinical disease, with few if any symptoms or signs. Clinical features may include the presence of a painless goitre, increased weight gain, growth retardation (in children), tiredness, lethargy, cold intolerance and bradycardia. Notably, goitre was less common in adults with type 1 diabetes than in the general population (Volzke et al 2007). Glycaemic control may not be significantly affected, although insulin requirements may be lower in hypothyroidism due to reduced insulin degradation. Hyperthyroidism may be associated with worsening glycaemic control and increased insulin requirements.

20.2.3 Screening and investigation

Screening tests for thyroid disease include measures of antibodies against TPO (TPOA) and thyroglobulin (TGA), and thyroid function tests (thyroid stimulating hormone [TSH], free T4 and T3). In the population without diabetes, TPOA is more specific than TGA, and TSH is the recommended screening test for thyroid disease. Hypothyroidism is confirmed by demonstrating a low free T4 level and a raised TSH concentration. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

Question 20.2

How and how often should people with type 1 diabetes be screened for thyroid disease?

The detailed systematic review of this question is in Chapter 20 of the accompanying technical report, and the evidence matrix is in Section C20 of Appendix C

The literature search identified six publications describing longitudinal screening for thyroid disease. These studies involved a total of 1127 children and adolescents and 464 adults with type 1 diabetes, screened on multiple occasions for thyroid disease and followed for up to 18 years (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Glastras et al 2005; Kordonouri et al 2005; Severinski et al 2009). Five of the studies were of moderate risk of bias and one of high risk of bias.

The method of screening included measurement of thyroid function (TSH, T4 and T3) in combination with measures of autoantibodies (TPOA and TGA) at diagnosis of type 1 diabetes. Follow-up screening with thyroid function tests alone was carried out in one study (Glastras et al 2005), and in combination with antibody testing in five studies (Perros et al 1995; Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009). Transient autoimmunity was only reported in one study in five children; in all cases, the initial TPOA and TGA titres were only slightly elevated (<100U/ml) (Kordonouri et al 2004). In the studies measuring thyroid antibodies at multiple time points, most people with positive thyroid antibodies were detected at the initial screening (Umpierrez et al 2003; Kordonouri et al 2004; Kordonouri et al 2005; Severinski et al 2009).

The studies demonstrated a high prevalence of thyroid autoimmunity and thyroid disease in type 1 diabetes. The prevalence of thyroid autoimmunity ranged from 5.4% to 15.5% in children and adolescents, and the prevalence of hypothyroidism was 8.1% in the study by Severinski (2009). In adults, the prevalence of thyroid disease, including subclinical disease, was reported as 12.4% in males and 31.4% in females (Perros et al 1995). In a cohort of Australian children, the incidence was 0.9 per 100 person years (Glastras et al 2005). By duration of diabetes, the cumulative incidence of autoimmune thyroiditis was reported as 14% after 10 years duration in children (Kordonouri et al 2005) and as high as 22% after

6 years duration in a group of Croatian children (Severinski et al 2009). In both studies, the cumulative incidence in girls was significantly greater than in boys. In adults, the annual incidence of thyroid disease was reported as 6.5% in males and 12.3% in females, including subclinical forms (Perros et al 1995).

Three studies, two in children and one in adults, reported statistically significant differences in the probability of developing thyroid disease between patients negative for thyroid antibodies at diagnosis of diabetes and those positive for antibodies; those with a positive screen were 17–18 times more likely to develop thyroid disease (Umpierrez et al 2003; Glastras et al 2005; Kordonouri et al 2005). Given the higher risk associated with the presence of autoantibodies, it may be appropriate to undertake a higher level of surveillance for this subgroup of patients.

The results of these studies provide the rationale for screening for thyroid disease at diagnosis of type 1 diabetes. The authors of these studies consistently recommended screening for thyroid disease at diagnosis of type 1 diabetes by measurement of thyroid function and thyroid autoantibodies.

For follow-up screening, three authors recommended annual thyroid function tests, particularly in those patients with an initial positive thyroid autoantibody test (Perros et al 1995; Umpierrez et al 2003; Glastras et al 2005); one study recommended bi-annual thyroid function tests in those initially negative to thyroid autoantibodies (Glastras et al 2005). Kordonouri et al (2005) recommended a combination of both thyroid function tests and thyroid autoantibody tests annually in those with a positive thyroid autoantibody test at diagnosis, and annually from onset of puberty in those with an initial negative thyroid autoantibody test. Severinski et al recommend annual screen with a thyroid autoantibody test and in those with a positive result, thyroid function tests (Severinski et al 2009).

The evidence is generalisable to both children and adults with type 1 diabetes with the only exclusions reported as those patients who had developed thyroid disease prior to the diagnosis of diabetes. The results are applicable to the Australian population with one study carried out in a cohort of Australian children and all other studies carried out in countries with a well-developed health-care system.

20.2.4 Management

Treatment of thyroid disease in type 1 diabetes is the same as that used in the general population. Hypothyroidism is treated with oral L-thyroxine sufficient to normalise TSH levels. Treatment of hyperthyroidism is usually with anti-thyroid drugs such as carbimazole or propylthiouracil; carbimazole is the preferred treatment in children due to the increased risk of liver failure in patients treated with propylthiouracil (Rivkees and Mattison 2009). Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis, to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radioactive iodine.

Evidence statements	
Q20.2	Thyroid dysfunction is common in type 1 diabetes, and positive antibodies are strongly predictive of thyroid dysfunction.
Recommendation	
R20.2	Screening for thyroid dysfunction and testing for antibodies to thyroid peroxidase (TPO Ab) should be performed at diagnosis of type 1 diabetes; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).
Practice points	
PP20.2.1	Tests for TSH should be repeated at least yearly in those with anti-thyroid antibodies at diagnosis.
PP20.2.2	Tests for TSH should be repeated at least 2-yearly in all other patients with type 1 diabetes.
PP20.2.3	Women planning pregnancy should have a blood test for TSH preconception and in the first trimester.
PP20.2.4	Women who are TPO Ab positive should be tested postpartum for thyroid dysfunction.
TPO, thyroid peroxidase; TSH, thyroid stimulating hormone	

21 Future research

The systematic reviews for these guidelines highlighted a lack of high-quality evidence in a number of areas related to clinical care of people with type 1 diabetes. In particular, many of the studies lacked statistical power to detect treatment effects, or had other methodological weaknesses. For many questions, there was no high-level evidence (Level II or III studies). Further research is needed to provide a stronger evidence base.

This chapter:

- describes the evidence gaps identified for questions and suggests areas for future research
- identifies topics that were not systematic reviewed, but may be considered in future revisions of these guidelines.

21.1 Evidence gaps and areas of future research

21.1.1 Natural history of type 1 diabetes

Question 3.1

What interventions delay or prevent the onset of type 1 diabetes?

There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes. Further studies are needed to investigate the effectiveness of therapies targeting both primary and secondary prevention. In particular, characterisation of subgroups of individuals with type 1 diabetes, by their genetic predisposition or environmental triggers, and identification of biomarkers in the prediabetes phase, may assist in targeted prevention strategies.

21.1.2 Characteristics of type 1 diabetes

Question 4.1

Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the lifespan, including clinical depression, anxiety disorder and eating disorder?

There is Level I evidence demonstrating that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups (women and the newly diagnosed), and an increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes, compared to the general population. Thus, longitudinal cohort studies, with appropriate controls, are needed to better understand the incidence of and risk factors for psychological morbidity among people with type 1 diabetes.

21.1.3 Blood glucose monitoring

Question 6.1

Does continuous real-time continuous glucose monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?

There is insufficient evidence to support routine use of continuous glucose monitoring (CGM) systems to improve glycated haemoglobin (HbA_{1c}) and reduce severe hypoglycaemia, although there is some evidence for a benefit in those with poorly controlled diabetes. In

this era of rapidly evolving technology, future studies should address the benefits of real-time CGM in specific patient populations, such as those with hypoglycaemia unawareness, recurrent severe hypoglycaemia or suspected nocturnal hypoglycaemia. Cost-effectiveness should also be addressed.

21.1.4 Insulin and pharmacological therapies

Question 7.2

(i) How effective are modern pumps versus multiple daily injections at reducing hypoglycaemia and HbA_{1c} and improving quality of life?

(ii) How effective are sensor-augmented insulin-infusion pumps versus multiple daily injections at reducing hypoglycaemia and HbA_{1c}, and improving quality of life?

There is no evidence to support a reduction in severe or nocturnal hypoglycaemia in children or adults. Many of the studies excluded individuals with a history of severe hypoglycaemia. Overall, the rate of severe hypoglycaemia and patients with hypoglycaemia unawareness is low, and the studies were not powered for the outcome of severe hypoglycaemia. Future studies should be powered to address the outcomes of severe and nocturnal hypoglycaemia.

Only one study was identified that examined the effectiveness of sensor-augmented pumps on metabolic outcomes. The study was not powered to address the outcome of severe hypoglycaemia, and quality of life (QoL) was not assessed. Future studies should examine the effects of sensor-augmented pumps on other outcomes relevant to individuals with type 1 diabetes, and whether they are of particular benefit to specific populations (e.g. young children, pregnant women).

Question 7.3

How effective is metformin plus insulin versus insulin alone at achieving glycaemic control (HbA_{1c} targets), reducing body weight, and reducing insulin requirement?

Level I evidence demonstrates a small but not statistically significant reduction in HbA_{1c} with metformin plus insulin compared to insulin alone; however, there was significant heterogeneity between studies. There have been no rigorous, prospective studies of metformin in type 1 diabetes, in relation to diabetes complications outcomes. Future studies should address the effects of metformin in specific populations (e.g. those with high insulin requirements), and the effect on microvascular and cardiovascular events and mortality in overweight people with type 1 diabetes.

21.1.5 Health care delivery

Question 8.2

What is the effectiveness of telemedicine and other technology-based delivery?

The systematic review found there is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings. The included studies reported were from international sources and were of limited methodological quality, involving small numbers of participants. Future studies should be relevant to the Australian health care system, relevant to contemporarily available technology and address outcomes for other populations, as well as rural and remote individuals.

21.1.6 Education and psychological support

Question 9.1

What is the diagnostic performance of the following screening tools: CDI, BASC, EDE, CHQ, BAI, BDI, HADS, EDI, ADS, ATT19?

ADS, Appraisal of Diabetes Scale; ATT19, Diabetes Integration Scale; BAI, Beck Anxiety Inventory; BASC, Behaviour Assessment System for Children; BDI, Beck Depression Inventory; CDI, Children's Depression Inventory; CHQ, Child Health Questionnaire; EDE, Eating Disorders Examination; Eating Disorder Inventory, EDI, HADS, Hospital Anxiety and Depression Scale

The systematic review found few studies that address this question, and the Expert Advisory Group (EAG) concluded that there is insufficient evidence to recommend any specific tool for psychological screening. Future studies should examine the diagnostic performance of screening tools in young people and adults with type 1 diabetes, and the benefits of screening on glycaemic control and psychosocial outcomes.

Question 9.2

What is the effectiveness of education and/or psychological support programs in type 1 diabetes:

- i) on metabolic outcomes
- ii) on psychological outcomes?

The systematic review did not examine the role of peer or social support programs. Future studies should examine the effects of such interventions in type 1 diabetes on metabolic and psychological outcomes.

21.1.7 Complementary and alternative medicines

Question 12.1 (interventional)

What is the effectiveness of complementary and alternative medicines at achieving metabolic targets?

Only four randomised controlled trials (RCTs) were identified that examined the effectiveness of complementary and alternative medicine (CAM) on metabolic outcomes and diabetes complications were not included as an outcome. Given the wide use of CAM in the community, future versions of this guideline should examine the effects of CAM on complications (e.g. gamma-linolenic acid on neuropathy). Future RCTs should study effectiveness on glycaemic control and diabetes complications, for types of CAM that have demonstrated benefit in short-term studies as potent insulin sensitisers or agonists.

21.1.8 Maternal pregnancy and fetal outcomes

Question 13.1

What is the effectiveness of preconception care in women with type 1 diabetes on improving maternal and fetal outcomes?

The systematic review found Level III evidence that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA_{1c} levels in women with type 1 diabetes. Future studies should consider other maternal and fetal outcomes (e.g. birth weight, macrosomia, pre-eclampsia or the risk of severe hypoglycaemia).

Question 13.2

What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?

There is insufficient evidence to make recommendation about the effectiveness of blood glucose control during pregnancy in achieving outcomes. Future studies need to address the benefit-to-risk ratio of very tight and less tight glycaemic control during pregnancy.

21.1.9 Contraception**Question 14.1**

What is the effectiveness of hormonal versus nonhormonal contraception in type 1 diabetes?

The systematic review did not identify sufficient evidence to assess whether progesterone-only or combined oral contraceptives differ from nonhormonal contraceptives in their effects on glycaemia control, lipid metabolism and long-term diabetes-related complications. Further studies are needed to address these issues and the effects of hormonal contraception on diabetes complications.

21.1.10 Acute effects of hypoglycaemia and hyperglycaemia**Question 16.1**

What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?

The systematic review concluded that data are not well-established for the effects of acute hyperglycaemia on cognitive function, and there is much individual variation in threshold for effects and rate of recovery. Future research examining the specific effects of acute hyperglycaemia on cognitive function will inform future guidelines, particular in educational and work settings, and for driving.

Question 16.3

How can severe hypoglycaemia be prevented?

The systematic review identified Level II and Level IV evidence that specific educational interventions (e.g. blood glucose awareness training [BGAT]) reduce the rate of severe hypoglycaemia. However, the recommendation based on this evidence is most relevant to adults with type 1 diabetes who had previously experienced severe hypoglycaemia. In addition, no formal educational programs such as BGAT for those at high risk of severe hypoglycaemia, have been reported in Australia. Future studies should evaluate strategies for prevention of hypoglycaemia among all individuals with type 1 diabetes across their lifespans.

21.1.11 Sick day management and diabetic ketoacidosis**Question 17.1**

Does ketone monitoring prevent ketoacidosis or hospital admission?

The evidence for the effectiveness of blood ketone monitoring versus urine ketone monitoring for the prevention of diabetic ketoacidosis (DKA) or hospital admission is based on one RCT in children. No studies were found in adults aged over 22 years. The effectiveness of home blood ketone measurement in adults with type 1 diabetes on these

outcomes, or ketone measurement in specific populations with type 1 diabetes (e.g. use of continuous subcutaneous insulin infusion [CSII]), could be addressed by future research.

21.1.12 Diabetes complications

Question 18.2 (ii)

How effective are antihypertensive agents at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?

The systematic review found evidence that angiotensin converting enzyme inhibitors (ACEI) prevent progression of pre-existing nephropathy; however, evidence of their effect on the onset of nephropathy or retinopathy is lacking, and evidence on prevention of progression of retinopathy or autonomic neuropathy is inconclusive or limited. Future guidelines should address the effectiveness of ACEI for these other outcomes among individuals with type 1 diabetes, including adolescents.

Question 18.3

What is the effect of statins on lipid levels and cardiovascular outcomes in type 1 diabetes?

Level I and II evidence demonstrates that statins are effective at reducing total and low density lipoprotein (LDL) cholesterol in adults with type 1 diabetes. Future guidelines should include the effectiveness of statins on markers of early cardiovascular disease in adolescents, and help to better define the appropriate age of commencement of statins in people with type 1 diabetes.

Question 20.1

How and how often should patients with type 1 diabetes be screened for coeliac disease?

The systematic review identified evidence to support routine screening at the time of diagnosis of type 1 diabetes in children and repeated at follow up until the risk declines, although none of the studies were designed to address the optimal frequency of screening. No studies were performed in adults. Future guidelines should address the role and frequency of screening for coeliac disease in adults.

21.2 Topics for future consideration

21.2.1 Screening for type 1 diabetes

Interventions to delay or prevent the onset of type 1 diabetes were addressed by the systematic review for question 1; however, screening for type 1 diabetes was not covered in this guideline. Most people who develop type 1 diabetes do not have a first-degree relative with the disease, and the prevalence of positive islet autoantibodies among such individuals is generally less than 5%; thus, screening is not currently performed outside the research setting. If successful primary or secondary prevention therapies become available in the future, then the role of screening would be relevant to future clinical care guidelines for type 1 diabetes.

21.2.2 Experimental therapies aimed at curing type 1 diabetes

The guidelines did not address experimental therapies for type 1 diabetes, such as islet cell transplant, which are currently only used in a research setting. As this field evolves, and if stem cell therapy becomes a therapeutic option, such treatment may become established in regular clinical care.

21.2.3 Maternal pregnancy and fetal outcomes

The guidelines did not address every aspect of clinical care in pregnancy in type 1 diabetes. Future guidelines should examine the evidence for intensive management (e.g. use of CSII) and monitoring (e.g. CGM) on maternal and fetal outcomes, optimal frequency for complications screening during pregnancy, management of delivery and its timing and postpartum management of the mother and infant.

21.2.4 Transition care

Transition care was not addressed in the guidelines due to the publication of best practice guidelines for transition (Lang 2008). However, further guidelines should address the optimal timing for transition of young people to adult care and models to improve uptake and continuity of care following transition.

21.2.5 Reduced hypoglycaemia unawareness

As people with reduced hypoglycaemia awareness are at high risk of recurrent severe hypoglycaemia, research into the mechanism of its development, methods to efficiently screen for its presence in the clinic, and approaches to minimising its impact should be addressed in future studies and guidelines.

21.2.6 Complications

The optimal frequency of complications screening was not systematically reviewed. Future research that examines tailoring of screening based on risk profiling (e.g. genetic or metabolic) would inform current guidelines, which are predominantly evidence based.

Systematic review of technologies to better define microvascular complication risk and preclinical markers may enable recommendations for complications screening to be individualised.

Medications that demonstrate benefit in complications in type 2 diabetes such as fenofibrate and metformin, should be clinically trialled in people with type 1 diabetes, for effects on diabetes microvascular and macrovascular outcomes.

There are no evidence-based recommendations for screening for macrovascular disease in people with type 1 diabetes; as this is an evolving area of research, future guidelines should address the optimal methods and frequency of screening.

There are no predictive tools based on risk-factor profiles for cardiovascular outcomes in type 1 diabetes. Such tools would be desirable to help identify individuals at highest risk and should include diabetes, renal status, age, blood pressure and lipid status.

21.2.7 Foot care

The foot guidelines (Baker IDI Heart and Diabetes Institute et al 2010; Baker IDI Heart and Diabetes Institute et al 2011) identified a number of areas for future research about foot care in people with diabetes. Of these, most are relevant to individuals with type 1 diabetes, in particular:

- drugs for the improvement of microvascular blood flow
- the effect of herbal or nutritional supplements on ulcer healing or amputation
- thermal wound therapy in addition to standard wound care
- educational programs for the prevention of ulcer recurrence and amputation.

22 Implementing, evaluating and maintaining the guidelines

22.1 Guidelines dissemination

The Expert Advisory Group (EAG), together with the Australian Diabetes Society (ADS) and the Australasian Paediatric Endocrine Group (APEG), have developed a strategy for extensive communication on the implementation of this guideline. The strategy identifies target audiences for the guidelines (health care professionals in the hospital and ambulatory care setting), tools for effective implementation (electronic, i.e. web-based, CDROM and paper; and presentations to target audiences), communication channels and key messages.

These are the first national, evidence-based guidelines to address the needs of individuals with type 1 diabetes across the lifespan. Thus, it is essential to engage societies of related disciplines (e.g. Australian Diabetes Educators Association, Australian Diabetes In Pregnancy Society, Dietitians Association of Australia, Pharmacy Guild of Australia, Royal Australian College of General Practitioners and Royal Australian College of Physicians) and consumer groups (e.g. Australian Diabetes Council, Diabetes Australia, Juvenile Diabetes Research Foundation and Type 1 Diabetes Network). These organisations will be asked to endorse the guidelines and to provide a link to the document from their websites. Communication to members of these organisations, in the form of e-casts, in newsletters and presentations and local and national meetings of these organisations, as appropriate, will be undertaken.

The public consultation process was helpful in formulating the plan for dissemination of the guidelines. The feedback proforma provided as part of the public consultation included a request for comment on dissemination of the guidelines (including suggested methods, other organisations to target in dissemination and key topics for dissemination). A number of these suggestions have been included in the implementation plan, for example targeting professional and consumer organisations and holding a workshop involving stakeholders.

The implementation and dissemination plan for the guidelines will also include:

- Specific targeting of recommendations that should have priority for implementation (among the questions that have been systematically reviewed and led to evidence-based recommendations), including timely diagnosis of type 1 diabetes, sick day management, hypoglycaemia management and management of complications.
- Addressing recommendations that will affect or deviate from current clinical practice. Overall, the evidence-based recommendations in the guidelines would not lead to significant changes in clinical care (including new technologies). However, the recommendations and practice points given in the guidelines are likely to enhance aspects of care in areas such as psychological care of children and youth, metformin in type 1 diabetes, indications for statin therapy, blood glucose awareness training for those at high risk of severe hypoglycaemia and blood ketone testing as part of sick day management. These will be highlighted during implementation.
- Addressing resource implications with the new recommendations and cost-effectiveness data, and indicate where a change in service delivery will be required as a result of a recommendation. Economic issues were considered when formulating the evidence-based recommendations, and they are unlikely to have major cost implications. Thus, cost is not expected to be a barrier to implementation of the recommendations.

- Developing partnerships with key organisations, including health professional organisations and type 1 diabetes related consumer organisations noted above, to assist with dissemination. This will be achieved through (i) regular communication with the organisations and their members regarding dissemination and (ii) inviting representatives from these organisations to attend a guideline dissemination and implementation workshop, planned for the latter half of 2011.
- Developing a concise handbook version of the guideline, which will contain recommendations, practice points and flow charts for key areas such as diagnosis of type 1 diabetes, insulin therapy, blood glucose monitoring, management of sick days and complications screening/management. We will also develop an electronic version of this (in the form of a webpage, as well as a pdf and CDROM) and will work the RACGP's software providers so that an electronic version is available on the GP's taskbar.
- Working with the RACGP to incorporate the summary version, recommendations and practice points into the Diabetes Handbook for GPs.
- Working with the EAG members to publish systematic reviews and key messages from the guidelines in the medical literature.
- Developing a plan for ongoing re-evaluation to monitor the impact of the guidelines, reduce variation in practice patterns and optimise effectiveness of clinical care.

22.2 Guidelines effectiveness assessment

Once the guidelines have been disseminated, continued re-evaluation will be necessary to monitor the impact of the guidelines, reduce variation in practice patterns and optimise effectiveness of clinical care. We also plan to evaluate implementation of the guidelines and to determine:

- the extent to which the guidelines influence changes in clinical practice and health outcomes
- what factors (if any) contribute to noncompliance with the guidelines.

The results of the evaluation will be used to inform future review of the guidelines.

22.3 Guidelines review and updating

The guidelines will be reviewed and amended in 5 years, unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need to review the document earlier.

APEG and ADS plan to convene a group of experts to undertake the review. In the intervening period, the co-chairs, via the secretariats of APEG and ADS, will be the contacts for major issues, events or practice changes.

To provide feedback and inform future reviews of these guidelines, comments on its content or implementation, or on the accompanying materials, should be sent to:

APEG Secretariat, PO Box 180, Morisset NSW 2264

Email: apeg@willorganise.com.au or Tel: 02 4973 6573, or

ADS Secretariat, 145 Macquarie Street, Sydney NSW 2000

Email: suzie@diabetessociety.com.au Tel: 02 9256 5462

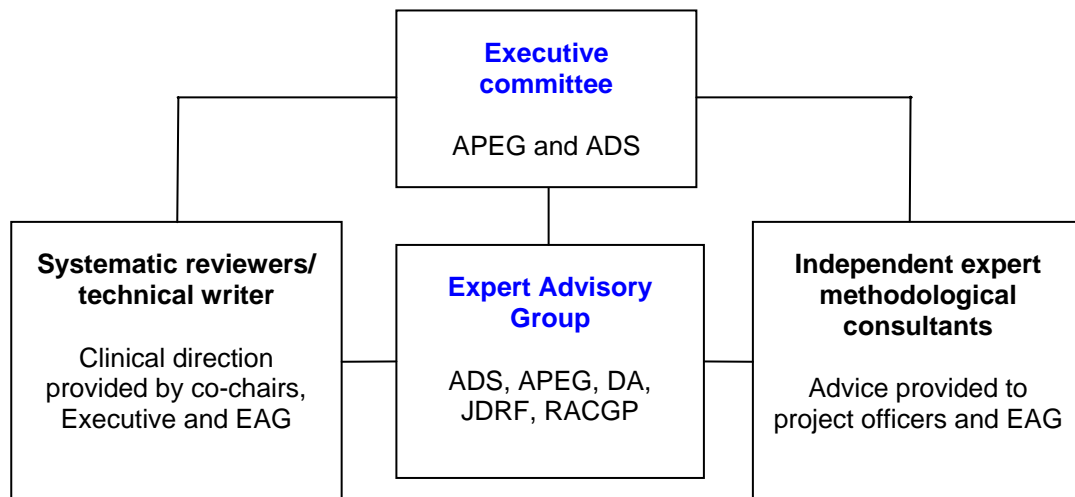
A list of colleges and societies that endorse the guidelines will be available on the APEG and ADS websites.

Appendix A: Governance

A1 Management structure for guideline development

Figure A1 illustrates the management structure for the development of the guidelines.

Figure A1 Management framework for development of the guidelines



ADS, Australian Diabetes Society; APEG, Australian Paediatric Endocrine Group; DA, Diabetes Australia; EAG, Expert Advisory Group; JDRF, Juvenile Diabetes Research Foundation; RACGP, Royal Australian College of General Practitioners

A2 Terms of reference

Executive

The Executive was established to provide coordination and direction for development of the guidelines. It was co-chaired by representatives from the Australian Diabetes Society (ADS) and the Australian Paediatric Endocrine Group (APEG). The role of the Executive was to:

- develop and oversee the project plan for the guidelines, and ensure that the development process meets National Health and Medical Research Council (NHMRC) requirements (NHMRC 2007)
- recommend the membership of the Expert Advisory Group (EAG), in consultation with APEG and ADS
- ensure effective communication and consultation with all relevant stakeholders for the duration of the project
- provide regular updates on the project to APEG and ADS councils and the Australian Government Department of Health and Ageing (DoHA)
- review resources that are dedicated to the project, to ensure that they are sufficient for the project to meet its deadlines

- review and approve revisions to the project plan
- address other matters as raised by members of the EAG

Expert Advisory Group

The EAG was formed to determine the scope and structure of the guidelines, and to determine the focus of the systematic review of the evidence-based literature. The group's terms of reference were to:

- consider the scope of the project and proposed structure of the guidelines, as referred by the Executive and, if necessary, to present to the Executive recommendations for revisions
- formulate the clinical questions to be answered by the literature review, under the guidance of the independent expert methodological consultants
- provide clinical oversight for the development of the content of the guidelines, in particular, ensuring that:
 - the research undertaken is comprehensive
 - the quality of the revised guidelines will meet with clinical approval
- ensure appropriate engagement by consumers at all relevant points
- assist in the development or review of tools and strategies to support the implementation and audit of the guidelines and review their uptake
- facilitate consultation and the uptake of the guidelines
- respond to any additional requirements to ensure compliance with the NHMRC guidelines development processes.

Systematic reviewers and technical writer

Project officers were appointed by APEG and ADS to conduct systematic reviews of the scientific literature, and to produce technical reports for the technical document. A technical writer was appointed to provide medical and technical editing.

Expert methodological consultants

Two guideline method advisors were appointed by the executive to provide advice and mentoring to the project officers and the EAG, and to ensure that the development process and guidelines complied with NHMRC requirements (NHMRC 2007).

Executive and operational support

The EAG secretariat was provided jointly by APEG and ADS. The secretariats provided support in communication, coordination of meetings, minute-taking and other administrative roles.

A3 Membership of bodies involved in governance of the guidelines

Co-chairs

Associate Professor Maria Craig	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Professor Stephen Twigg	Endocrinologist	Australian Diabetes Society

Executive

Professor Fergus Cameron	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Associate Professor N Wah Cheung	Endocrinologist	Australian Diabetes Society
Dr Jenny Conn	Endocrinologist	Australian Diabetes Society
Professor Kim Donaghue	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Associate Professor Alicia Jenkins	Endocrinologist	Australian Diabetes Society
Professor Martin Silink	Paediatric endocrinologist	Australasian Paediatric Endocrine Group

Expert Advisory Group

Dr Linda Beeney	Psychologist	Independent psychological expert
Professor Stephen Colagiuri	Endocrinologist Medical Advisor	Australian Diabetes Society
Dr Louise Conwell	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Professor Jenny Couper	Paediatric endocrinologist	Australian Diabetes Society
Ms Nuala Harkin	Nurse practitioner	Australasian Paediatric Endocrine Group, Australian Diabetes Educators Association
Professor Mark Harris	General practitioner	Royal Australian College of General Practitioners
Ms Heather Hart	Credentialed diabetes educator	Australian Diabetes Society, Australian Diabetes Educators Association

Dr Jane Holmes-Walker	Endocrinologist	Australian Diabetes Society
Dr Craig Jefferies	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Dr Tony Lafferty	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Ms Eunice Lang	Credentialed diabetes educator	Australasian Paediatric Endocrine Group
Clinical Professor Tim Jones	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Ms Kate Marsh	Accredited Practising Dietitian	Australian Diabetes Society
Dr Alison Nankervis	Endocrinologist	Australian Diabetes Society, Australian Diabetes in Pregnancy Society
Dr Mark Pascoe	Paediatrician	Australasian Paediatric Endocrine Group
Associate Professor Christine Rodda	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Dr Tony Russell	Endocrinologist	Australian Diabetes Society
Ms Carmel Smart	Accredited Practising Dietitian	Australasian Paediatric Endocrine Group
Ms Renza Scibilia	Consumer	Diabetes Australia
Ms Chantelle Stowes	Consumer	Juvenile Diabetes Research Foundation, Australia
Dr Helen Woodhead	Paediatric endocrinologist	Australasian Paediatric Endocrine Group
Associate Professor Sophia Zoungas	Endocrinologist	Australian Diabetes Society

Project officers

Dr Kerri-Ann Clayton	Endocrinology Registrar, Royal Prince Alfred Hospital
Mr Daniel Davies	The University of Sydney
Ms Maria Gomez	The University of Sydney
Ms Helen Phelan	Credentialed Diabetes Educator, John Hunter Children's Hospital

Expert methodological consultants

Dr Sarah Norris Health Technology Analysts

Dr Lisa Elliot Health Technology Analysts

Secretariat

Ms Suzie Neylon Australian Diabetes Society Secretariat

Ms Lyndell Wills Australasian Paediatric Endocrine Group Secretariat

Medical writer

Dr Hilary Cadman Cadman Editing Services

Conflict of interest

All members of the EAG declared any conflicts of interest before starting work on the guidelines. Conflicts of interest were also reviewed and updated at the commencement of all EAG meetings and at completion of the guidelines. Declarations were made to the Co-chairs of the EAG through the guideline secretariats. Written guidelines for declaring conflicts of interest were provided to the EAG members, who were informed of the responsibility of the individual to identify and disclose any real or potential conflict of interest in relation to the content of the guidelines or guideline recommendations.

A5 Acknowledgements

The ADS and APEG received funding from DoHA to review and update the guidelines for the care of children and adolescents with type 1 diabetes, and to extend the guidelines to address the needs of adults with type 1 diabetes.

The EAG also wishes to acknowledge editorial assistance provided by Ms Trisha Dunning and Dr Elizabeth Northam, and input during the guideline development process from Ms Kate Gilbert, on behalf of the Type 1 Diabetes Network.

Appendix B: Process report

B1 Development process

Due to a lack of national evidence-based guidelines for management of type 1 diabetes across the lifespan, the Australasian Paediatric Endocrine Group (APEG) and the Australian Diabetes Society (ADS) agreed to review and update the type 1 diabetes guidelines in children and adolescents (APEG 2005) and to extend the guidelines to address the needs of adults with type 1 diabetes, on behalf of the Australian Government Department of Health and Ageing (DoHA). In 2009, an Executive Advisory Group (EAG) was formed to oversee development of the guidelines. Members of the EAG were nominated by APEG and ADS councils to represent APEG, ADS, the Australian Diabetes Educators Association (ADEA), the Australian Diabetes In Pregnancy Society (ADIPS) and the Dietitians Association of Australia (DAA). Representation from the Royal Australian College of General Practitioners (RACGP) and consumer organisations – Diabetes Australia (DA) and the Juvenile Diabetes Research Foundation (JDRF) – were also invited. Further details of the governance framework are provided in Section 1.2 and Appendix A.

B2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EAG from July 2009 to March 2010, and further refined through consultation among the systematic reviewers and expert methodological consultants. A technical report, which contained the systematic reviews, was developed before the writing of the guidelines.

B3 Methodology

Methods are outlined in Chapter 2, with greater detail given of each systematic review in the accompanying technical report. Briefly, the clinical research questions for systematic review were structured using PICO ('population, intervention, comparator and outcome' for intervention questions), PPO ('population, predictor and outcome' for prognostic questions) or PRO ('population, risk factor and outcome' for aetiological questions) criteria. Three main strategies were identified potentially relevant literature: electronic database searching, manual searching and literature recommended by expert members of the EAG. The primary databases searched were EMBASE, Medline and the Cochrane Library Database. Additional searches were conducted of Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published between June 1966 and December 2010.

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated as detailed in the *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines* (NHMRC 2009). An NHMRC evidence statement form was completed for each systematically reviewed research question (see Appendix C). Studies were assessed for study quality as outlined in Chapter 2 (Section 2.2.2) (NHMRC2000).

Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation (NHMRC 2009). Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was

required to supplement recommendations and guide clinical practice, the EAG developed practice points through a consensus-based process. If the EAG felt there was not enough expertise in the room, it was determined what else was required and in some cases this involved seeking professional opinion from expert organisations. The development of practice points by consensus is shown below (Figure A1).

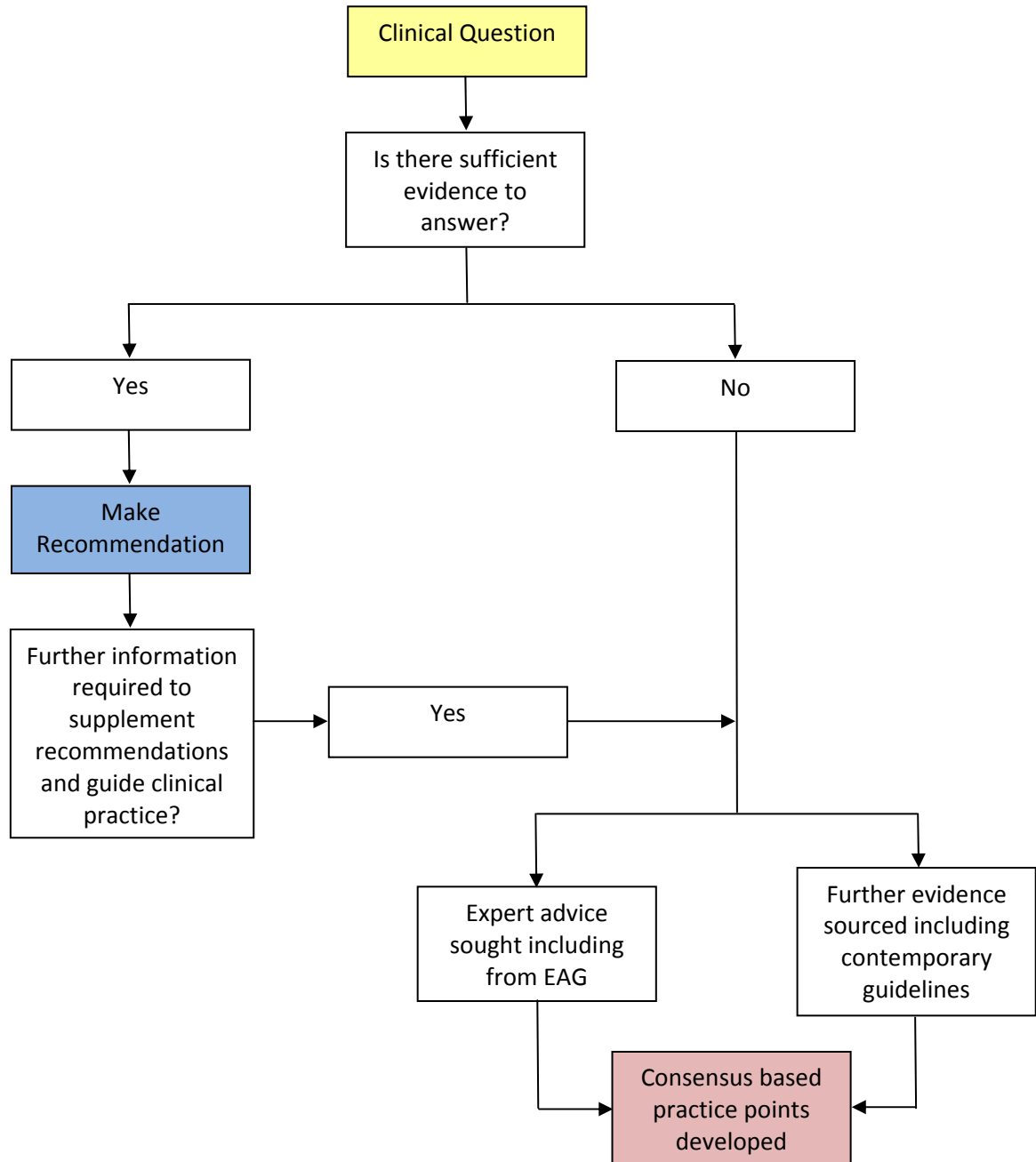


Figure A1: Process for development of practice points

Materials relevant to the narrative sections (that were not systematically reviewed) were gathered by the project officers under the supervision of the EAG members. Sources included contemporary evidence based guidelines, medical textbooks, published scientific and review articles, and other relevant medical literature; however, systematic review processes were not applied. The sections and chapters researched in this manner are noted throughout the guideline and the source of the information noted.

B4 Public consultation

Public consultation was conducted from Monday 7 February to Friday 11 March 2011, during which time the draft guidelines were available on the APEG and ADS websites. Notification was posted in *The Australian* national newspaper, and the APEG and ADS invited a range of stakeholders, committees, working groups and interested people to provide submissions. An electronic feedback form was provided to facilitate submissions.

Key stakeholder organisations notified directly by email of public consultation and requested to comment were:

- Australian Diabetes Society (ADS)
- Australian Diabetes Educators Association (ADEA)
- Australasian Diabetes in Pregnancy Society (ADIPS)
- Australasian Paediatric Endocrine Group (APEG)
- Australian Psychological Society (APS)
- Australian Diabetes Council (ADC)
- Diabetes Australia (DA)
- Dietitians Association of Australia (DAA)
- International Diabetes Federation (IDF)
- Juvenile Diabetes Research Foundation (JDRF)
- Royal Australian College of Physicians (RACP)
- Royal Australian College of General Practitioners (RACGP)

As a result of the consultation process 36 submissions were received. The issues raised in these submissions were considered carefully and consulted about internally and externally by the guideline developers.

B5 Finalising the guidelines

Following public consultation and amendments to the guidelines and technical report, the final draft of the guidelines were reviewed by the EAG co-chairs (Associate Professor Maria Craig and Professor Stephen Twigg) and EAG members to assess compliance with NHMRC requirements for externally developed guidelines (NHMRC 2007).

Appendix C: Evidence matrices

Question 3.1

Question 3.1 – nicotinamide

Q3.1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Four RCTs, all of good quality.
Consistency	A	Studies consistent in showing no effect.
Clinical impact	NA	Given that nicotinamide is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 3 of the accompanying technical report	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 3.1 – insulin

Q3.1	What interventions delay or prevent the onset of type 1 diabetes?	
Evidence statement	There is no evidence to support the use of any intervention to delay or prevent the onset of type 1 diabetes.	
Evidence base	A	Five RCTs – three of low risk of bias, one of moderate risk of bias and one of high risk of bias.
Consistency	A	All studies reporting diabetes as an outcome were consistent (excluding the one poor-quality study).
Clinical impact	NA	Given that insulin is not used routinely to delay or prevent type 1 diabetes, the clinical impact of this intervention is not applicable.
Generalisability	C	The target population was people without type 1 diabetes. The evidence base included only high-risk populations (but with differences in definitions), who represent only 10% of people who develop type 1 diabetes.
Applicability	A	The studies included one from Australia; the remainder were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 3 of the accompanying technical report	
Recommendation		
R3.1	No interventions are recommended for use in clinical practice to delay or prevent the onset of type 1 diabetes (Grade A).	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 4.1

Q4.1	Is there an increased prevalence of psychological disorders in people with type 1 diabetes across the life span, including clinical depression, anxiety disorder and eating disorder?	
Evidence statement	<p>Level I evidence shows that the prevalence of depression in people with type 1 diabetes is greater in certain subgroups – women and the newly diagnosed – than in the general population.</p> <p>Level I evidence shows that there is increased prevalence of bulimia nervosa in adults and adolescents with type 1 diabetes compared to the general population.</p> <p>Level II evidence indicates that there are higher referral rates to mental health services in children and young adults with type 1 diabetes, compared with the general population.</p> <p>Level IV evidence shows an increased prevalence of depression and anxiety in young people and adolescents with type 1 diabetes, compared with the general population.</p> <p>Level IV evidence shows that the prevalence of anxiety in adults with type 1 diabetes is high, but similar to that in the general population.</p>	
Evidence base	A	<ul style="list-style-type: none"> • Eating disorders: Two Level I, one Level II and two Level IV studies, (adolescent and adult). • Depression: One Level I and one Level IV studies (adults); one Level II study (paediatric) (no control group). • Anxiety: One Level I study (adults), two Level IV studies (one paediatrics, one adult). • Psychosocial: One Level IV study (adults), two Level II studies and one Level IV study (paediatrics).
Consistency	B	<ul style="list-style-type: none"> • Psychosocial: Increased rate of referral to mental health services in paediatrics and adolescents (one Level II study); no differences in psychological adjustment and psychosocial difficulty in one Level II and one Level IV study in paediatrics and adolescents. • Depression: No difference in Level I study, but a significant difference in Level IV study (adults). • Anxiety: Not applicable (adults, one study only); studies uncontrolled (paediatrics). • Eating disorders: Anorexia – no difference in both Level I studies; bulimia – increased in both Level I studies (adults and adolescents); Level IV studies showed increase prevalence of disordered traits in type 1 diabetes, but no difference in diagnosed eating disorders (adolescents).
Clinical impact	C	Adults.
	A	Children and adolescents.
Generalisability	A	Paediatric, adolescent and adult populations were delineated in most studies.
Applicability	B	Studies were from North America and Europe; thus, they were from countries with well-established health-care systems.
Other factors	None identified.	
Details	For full systematic review, see Chapter 4 of the accompanying technical report	
Recommendation		
R4.1	Clinicians should be aware that the co-occurrence of psychological disorders in type 1 diabetes is common (Grade A).	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 4.2

Q4.2		What is the impact of type 1 diabetes on cognitive performance?
Evidence statement	Evidence from Level I and II studies show a longitudinal association between glycaemic control and some aspects of cognitive function. The magnitude of this effect is greatest in children with early onset type 1 diabetes.	
Evidence base	B	Three Level II studies (two of low risk of bias, one of moderate risk of bias), and two Level IV studies, both of high risk of bias.
Consistency	B	Compared with healthy controls, children and adolescents demonstrated marginal effect on several domains and scored marginally lower on IQ, but with no effect on learning and memory. Adults demonstrated a small-to-moderate effect on several cognitive domains, again with no effect on learning and memory. Hypoglycaemia predicts a lower verbal IQ in children (one study), with no other significant effect reported. In relation to metabolic control, a higher HbA _{1c} is associated with a negative impact on cognitive function (reported in two studies including children >9 years, adolescents and adults). One study reported no significant effect on IQ. In early-onset diabetes, a negative association was reported in one prospective study and one meta-analysis.
Clinical impact	A	Children.
	B	Adolescents and adults.
Generalisability	B	Studies included children, adolescents and adults. Exclusions included diabetes complications, history of head trauma and depression. There is no evidence from the older adult or the elderly population (especially with respect to dementia).
Applicability	A	One study was in Australian children, two were from the United States (i.e. a country with a well-established health-care system).
Other factors	The mechanism is not known.	
Details	For full systematic review, see Chapter 4 of the accompanying technical report	
Recommendation		
R4.2	To minimise the impact of diabetes on cognitive function, every effort should be directed toward achieving glycaemic targets (Grade B).	

HbA_{1c}, glycated haemoglobin; IQ, intelligence quotient

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 6.1

Question 6.1 – HbA_{1c}

6.1	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA _{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias. Systematic review comprised nine RCTs with a low or moderate risk of bias.
Consistency	C	There was significant clinical and methodological heterogeneity across the nine RCTs, but some consistency regarding the magnitude and direction of effect. There was a nonsignificant advantage to real-time monitoring, with the direction fairly consistent across studies. Children – limited evidence (two RCTs). Adolescents – two RCTs. Adults – consistent up to 6 months, but inconsistent beyond that time, possibly due to lack of adherence (six RCTs). All age groups – (five RCTs).
Clinical impact	D	
Generalisability	C	Studies included children and adolescents, or adults, but some had a small sample size.
Applicability	B	The studies included one Australian study.
Other factors	Continuous real-time monitoring is not used routinely in Australia, but is a rapidly developing technology. The clinical role of real-time blood glucose monitoring is expected to increase with time; therefore, the current evidence statement may become outdated.	
Details	For full systematic review, see Chapter 6 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 6.1 – hypoglycaemia

Q6.1	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous real-time monitoring to improve HbA _{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	C	
Applicability	B	
Other factors	None identified.	
Details	For full systematic review, see Chapter 6 of the accompanying technical report	
Recommendation		
R6.1	Real-time CGM may be considered for individuals expected to adhere with therapy, but routine use is not currently recommended (Grade C).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 6.2

Question 6.2 – HbA_{1c}

Q6.2	Does continuous glucose monitoring (retrospective systems) versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA _{1c} and reduce severe hypoglycaemia.	
Evidence base	A	Level I evidence with a low risk of bias, comprising seven RCTs: three with a low risk of bias and four with a moderate risk of bias.
Consistency	C	There was a nonsignificant reduction in this outcome. A sensitivity analysis of the high-quality studies reduced the magnitude of the effect. A subgroup analysis of the paediatric group found a significant effect, but results in adults were conflicting.
Clinical impact	D	The magnitude of change in the meta-analysis was –0.4%.
Generalisability	B	
Applicability	B	The studies included one Australian study in children.
Other factors	None identified.	
Details	For full systematic review, see Chapter 6 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 6.2 – hypoglycaemia

Q6.2	Does continuous real-time monitoring versus standard management improve HbA_{1c}, minimise fluctuations of blood glucose and reduce severe hypoglycaemia?	
Evidence statement	There is insufficient evidence to support routine use of continuous retrospective blood glucose monitoring systems to improve HbA _{1c} and reduce severe hypoglycaemia.	
Evidence base	A	
Consistency	C	There were no reports of severe hypoglycaemia; there was insufficient evidence on this outcome, because studies lacked power due to low event rates.
Clinical impact	D	
Generalisability	B	
Applicability	B	
Other factors	None identified.	
Details	For full systematic review, see Chapter 6 of the accompanying technical report	
Recommendation		
R6.2	Retrospective CGM systems are not recommended for routine use to improve glycaemic control or reduce severe hypoglycaemia, but may be considered for children and adolescents (Grade C).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

C12 Question 7.1

Question 7.1 (i) – HbA_{1c}

Q7.1 (i) How effective are insulin analogues versus human insulin at reducing HbA _{1c} ?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with NPH insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.
Evidence base	C One good-quality systematic review (Level I evidence) was selected from 15 identified systematic reviews. The selected study was based on Level II evidence (17 RCTs) that was of poor quality (i.e. lack of double blinding and of ITT reporting). In addition, 3 RCTs (Level II) were included, all of which were of fair quality.
Consistency	B The RCTs included in the Level I study were mostly consistent, as were findings across all the Level I studies identified.
Clinical impact	D The reduction in HbA _{1c} was <i>statistically</i> significant, but was below the level commonly accepted as <i>clinically</i> significant (0.5% change in HbA _{1c}). Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B Patients characteristics were HbA _{1c} 6–11% at baseline, with some exclusions of HbA _{1c} below 10% or 11%. Many studies excluded patients for severe hypoglycaemia.
Applicability	A Studies included populations from Australia, Europe, South Africa and the United States and were thus from countries with well-established health-care systems.
Other factors	None identified.
Details	For full systematic review, see Chapter 7 of the accompanying technical report

HbA_{1c}, glycated haemoglobin; ITT, intention to treat; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.1 (i)– hypoglycaemia

Q7.1 (i) How effective are insulin analogues versus human insulin at reducing hypoglycaemia?	
Evidence statement	Compared with human insulin, insulin analogues have no effect on overall hypoglycemia, but lead to a slight reduction in severe and nocturnal hypoglycemia in adults. Compared with human insulin, insulin detemir shows a small but significant benefit with respect to nocturnal and overall hypoglycemia in children and adolescents.
Evidence base	C One good quality systematic review (Level I evidence) was identified, but the study was based on poor-quality Level II evidence (i.e. lack of double blinding and lack of ITT reporting).
Consistency	C The definitions of hypoglycaemia used in individual trials were not consistent. There was also variation in the units of measurement between trials. This resulted in high heterogeneity and it was thus not possible to make summary estimates for specific subgroups.
Clinical impact	D The clinical impact of hypoglycaemia is significant. However, evidence on the clinical impact was lacking, apart from in one subtype of hypoglycemia. Impact on patient satisfaction (which is considered to be a key benefit of analogues) was not captured by the Level I study selected.
Generalisability	B Patient characteristics: HbA _{1c} 6–11% at baseline, with some exclusions of HbA _{1c} <10 or <11. Many studies excluded patients for severe hypoglycaemia.
Applicability	A Studies included populations from Australia, Europe, South Africa and the United States.
Other factors	Impact of hypoglycaemia (and the associated disutility) not fully captured in the studies. Evidence base is missing the patient perspective.
Details	For full systematic review, see Chapter 7 of the accompanying technical report

HbA_{1c}, glycated haemoglobin; ITT, intention to treat

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.1 (ii)

Question 7.1 (ii) – HbA_{1c}

Q7.1 (ii) What is the relative effectiveness between insulin analogues on HbA _{1c} ?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA _{1c} .
Evidence base	C One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	A Different agents were compared; thus, the results could not be pooled.
Clinical impact	D The studies did not capture patient satisfaction or preference.
Generalisability	B The population was aged 20–40 years, HbA _{1c} was 7–8% at baseline, and severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.
Details	For full systematic review, see Chapter 7 of the accompanying technical report

EAG, Expert Advisory Group; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.1 (ii) – hypoglycaemia

Q7.1 (ii)	What is the relative effectiveness between insulin analogues at reducing hypoglycaemia?	
Evidence statement	Level II evidence is consistent in showing no significant difference between insulin analogues in relation to their effect on HbA _{1c} .	
Evidence base	C	One good-quality systematic review was identified that included two RCTs (Level II evidence) of fair and poor quality; three RCTs (Level II) of fair quality were also identified.
Consistency	C	One Level II study showed a significant difference in hypoglycemia rate between insulin analogues; the remaining four studies did not show a significant difference. The agents compared were different in all but two studies; thus, consistency was limited across the body of evidence.
Clinical impact	D	The studies did not capture patient satisfaction or preference.
Generalisability	B	Population was aged 20–40 years; HbA _{1c} was 7–8% at baseline; severe hypoglycaemia was an exclusion criterion in most studies.
Applicability	A	No Australian studies or sites were included in the studies, but the results are considered applicable to the Australian health-care context.
Other factors	Based on a literature review of economic evaluations of analogues, the EAG concluded that analogues are unlikely to be cost effective at the published prices in Australia. However, the true cost effectiveness has probably not been captured, because none of the published economic analyses captured the patient perspective.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	
Recommendation		
R7.1	Human insulin or insulin analogues may be used as treatment for glycaemic control (Grade C).	

EAG, Expert Advisory Group; HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.2

Question 7.2 – HbA_{1c}

Q 7.2		How effective are modern CSII versus MDI at reducing HbA _{1c} ?
Evidence statement	Across all individuals with type 1 diabetes, Level I evidence demonstrates a small but statistically significant reduction in HbA _{1c} with CSII compared to MDI. Level II evidence shows that CSII has a minor benefit for HbA _{1c} levels compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	B	The included studies were fairly consistent in relation to changes in HbA _{1c} , showing a statistical difference in favour of CSII.
Clinical impact	D	The accuracy of HbA _{1c} measurement is 0.2%; hence, the magnitude of the observed changes in adults was within the bounds of measurement error, but this was not the case for children and adolescents younger than 18 years.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Exclusions included severe hypoglycaemia, hypoglycaemia unawareness and complications of diabetes.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA _{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children and adolescents; modern pumps are defined as those that are available in Australia or overseas and are not obsolete.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.2 – hypoglycaemia

Q7.2	How effective are modern CSII versus MDI at reducing hypoglycaemia?	
Evidence statement	There is no evidence to support a reduction in hypoglycaemia in adults. There is Level I evidence of a slight, but statistically significant increase in mild hypoglycaemia in children using CSII. There is no statistically significant evidence to support a reduction in severe and nocturnal hypoglycaemia in adults and children.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias.
Consistency	C	Definitions of hypoglycaemia varied between studies, making comparisons difficult. In one systematic review, an evaluation of individual studies indicated no difference in nonsevere hypoglycaemia between groups, and a tendency towards less severe hypoglycaemia in the CSII group. In two other reviews, a meta-analysis of studies showed no difference between groups in relation to severe hypoglycaemia. In one systematic review, a meta-analysis of studies showed significantly more episodes of hypoglycaemia in children treated with CSII.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small. Some of the studies included in this systematic review had hypoglycaemia unawareness and one or more recent severe hypoglycaemia episodes as exclusion criteria.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA _{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children and adolescents; modern pumps are defined as those that are available in Australia or overseas and are not obsolete.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.2 – quality of life

Q7.2		How effective are modern CSII versus MDI at improving QoL?
Evidence statement	Level II evidence shows an improvement in QoL with CSII compared to MDI. Level II evidence consistently shows improved treatment satisfaction with CSII compared to MDI.	
Evidence base	C	One good-quality systematic review (Level I) was identified, but the study was based on Level II studies with a moderate to high risk of bias. Also, the systematic review included evidence with pumps that are now obsolete. The systematic review undertaken for these guidelines was updated and was limited to modern pumps; however, many of the included studies had a moderate risk of bias. QoL was poorly reported, and was measured using a variety of instruments. Results were not pooled.
Consistency	D	The results of the Level II studies were inconsistent in relation to QoL: <ul style="list-style-type: none"> • 7 studies (n=425) found statistical difference in favour of CSII • four studies (n=85) found no statistical differences between MDI and CSII. The results of the Level II studies were consistent where: <ul style="list-style-type: none"> • PedsQL was used • treatment satisfaction was measured.
Clinical impact	D	The clinical impact is unclear.
Generalisability	B	The meta-analysis conducted for the current systematic review included 697 patients. However, the individual studies were small, and the total sample for children younger than 5 years was very small.
Applicability	B	No studies were conducted in Australia. However, all studies were undertaken in countries with an established health-care system.
Other factors	A systematic search of the literature for published economic evaluations of insulin pumps found that pumps are typically only cost effective when the magnitude of change in HbA _{1c} is at least 0.51%. This sensitivity analysis is modelled on reductions in consequent diabetes complications over a lifetime horizon. A second cost-effectiveness analysis was based on the incremental costs per severe hypoglycaemia attack avoided over 6 years.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	
Recommendation		
R7.2	Nonsensor-augmented CSII should be considered for use in individuals in whom the expected magnitude of benefit is clinically significant in terms of reducing HbA _{1c} , reducing hypoglycaemia or improving QoL (Grade C).	

CSII, continuous subcutaneous infusion pumps; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injections; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life

Notes: MDI is defined as three injections per day for adults, and three or more injections per day for children; modern pumps are defined as those that are available in Australia or overseas and are not obsolete; QoL is defined as DQoL, SF-36 or others.

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.3

Question 7.3 – HbA_{1c}

Q7.3		How effective is metformin plus insulin versus insulin alone at achieving HbA _{1c} targets?
Evidence statement	Level I evidence demonstrates a small but not statistically significant reduction in HbA _{1c} with metformin plus insulin compared to insulin alone.	
Evidence base	C	One systematic review was identified that included nine RCTs (with a meta-analysis of five of the RCTs). Change in HbA _{1c} was an outcome reported in the meta-analysis.
Consistency	B	Most studies reporting this outcome were consistent. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on cost effectiveness of metformin in type 1 diabetes, but metformin is a low-cost drug.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.3 – body-mass index

Q7.3	How effective is metformin plus insulin versus insulin alone at reducing BMI or weight?	
Evidence statement	Level II evidence shows no consistent effect of metformin plus insulin versus insulin alone on reduction in BMI or body weight.	
Evidence base	C	One systematic review was identified that included nine RCTs with a moderate risk of bias; six of these RCTs reported changes in BMI or body weight.
Consistency	D	Metformin plus insulin versus insulin alone was associated with weight loss of 1.7–6.0 kg (mean of 1.74 kg in longest duration study), but three studies found no difference in weight. There were insufficient data on weight for the authors to conduct a formal meta-analysis of this outcome.
Clinical impact	D	Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B	Adults.
	C	Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children under 16 years of age).
Applicability	B	There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off-label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.	
Details	For full systematic review, see Chapter 7 of the accompanying technical report	

BMI, body-mass index; RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 7.3 – insulin requirements

Q7.3 How effective is metformin plus insulin versus insulin alone at reducing insulin requirements?	
Evidence statement	Level I evidence demonstrates a small but statistically significant reduction in insulin requirement with metformin plus insulin compared to insulin alone.
Evidence base	C One systematic review that included nine RCTs (with a meta-analysis of five of the RCTs). Insulin dose was an outcome reported in the meta-analysis.
Consistency	A All five studies reporting this outcome were consistent; overall, they showed a mean reduced insulin requirement of 6.6 U/day. The authors of the systematic review conducted a sensitivity analysis of the four smaller RCTs, excluding the largest RCT because of issues of heterogeneity. The outcome was confirmed in both analyses.
Clinical impact	D Benefit is small and therefore will have a restricted impact on clinical management. In addition, due to the small sample size, safety could not be adequately addressed.
Generalisability	B Adults.
	C Children and adolescents (the evidence base is limited by age and weight, and there is no evidence in children younger than 16 years).
Applicability	B There were no studies from Australia; however, all the studies were undertaken in countries with an established health-care system.
Other factors	Metformin is not TGA-approved for use in type 1 diabetes, so any current use is off label. There are likely to be issues with compliance, and with safety (especially lactic acidosis). There are no publications on economic populations in type 1 diabetes, but metformin is a low-cost drug.
Details	For full systematic review, see Chapter 7 of the accompanying technical report
Recommendation	
R7.3	Metformin should not be used in routine clinical practice for type 1 diabetes (Grade C).

RCT, randomised controlled trial; TGA, Therapeutic Goods Administration

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 8.1

Q8.1	What is the effectiveness of ambulatory care versus hospital inpatient care of people with newly diagnosed disease?	
Evidence statement	Ambulatory care, delivered by a multidisciplinary team in a tertiary referral diabetes service, at diagnosis of type 1 diabetes in children over 2 years of age: results in a lower HbA _{1c} (0.7%) at 3 years follow-up compared to in-hospital care at diagnosis does not increase the risk of severe hypoglycaemia or diabetic ketoacidosis, or result in poorer levels of diabetes knowledge at 2 years follow-up compared to in-hospital care at diagnosis.	
Evidence base	A	One Level II study (of low risk of bias) in children older than 2 years. One Level IV study (of high risk of bias) in children. One Level IV systematic review of low level of bias (included five studies in addition to the Level II study above – four of high risk of bias, one of medium risk of bias).
Consistency	B	<ul style="list-style-type: none"> • HbA_{1c} – one Level II study demonstrated 0.7% difference between groups in favour of home care. All other studies found no significant difference. • Severe hypoglycaemia – no significant difference (consistent). • Diabetic ketoacidosis – no significant difference (consistent). • Patient knowledge – no significant difference (consistent).
Clinical impact	B	Ambulatory care is as effective as inpatient care in terms of glycaemic targets, rates of severe hypoglycaemia and diabetic ketoacidosis, and diabetes knowledge.
Generalisability	C	No adults in evidence base, no children younger than 2 years
Applicability	C	Setting – One study was conducted in Australia, and the others in countries with an established health-care system. Evidence was from tertiary centres only, and may not be applicable to rural and remote settings.
Other factors	From Dougherty et al (1999): Parents in the home-based group spent significantly fewer hours on diabetes care and incurred significantly lower out-of-pocket expenses during the first month. Health-care sector costs were significantly higher. Hospital costs were \$889 higher, and government costs \$890 higher per child. Social (total) costs were only \$48 higher per case (nonsignificant) with home care, when parents' time was valued at \$11.88 per hour. Implementation issues: infrastructure, demographically appropriate.	
Details	For full systematic review, see Chapter 8 of the accompanying technical report	
Recommendation		
R8.1	Children and adolescents presenting with newly diagnosed type 1 diabetes should be managed in an appropriately resourced ambulatory care or inpatient hospital setting (Grade B).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 8.2

Q8.2		What is the effectiveness of telemedicine and other technology-based delivery methods for rural and remote individuals?
Evidence statement	There is insufficient evidence to determine the effect of telemedicine and other technology-based delivery methods for rural and remote individuals on glycaemic control or time and cost savings.	
Evidence base	D	Four studies: two Level II studies, one Level III study and one Level IV study; all with high risk of bias, in which telemedicine replaced standard care.
Consistency	C	One RCT found a significant reduction; three showed no effect.
Clinical impact	C	If compared to tertiary outreach.
Generalisability	B	Three in adults, one in children.
Applicability	C	In the study by Biermann et al (2000), the definition of remote was only 50 minutes to clinic. Most studies were either old or out of date.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	
Recommendation		
There was insufficient evidence to make a recommendation.		

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9.1

Q9.1		Psychological screening tools
Evidence statement	There is one Level II and one Level III study demonstrating the diagnostic accuracy of the BDI in a mixed population of type 1 and type 2 diabetes. There is one Level II study examining the diagnostic accuracy of the CHQ administered to the parents of children with type 1 diabetes. No evidence was identified for the performance of other psychological screening tools in type 1 diabetes.	
Evidence base	C	Two Level II studies (diagnostic accuracy) of fair quality and one Level III-II study (diagnostic accuracy) of fair quality.
Consistency	B	Studies were broadly consistent, with difference related to instruments.
Clinical impact	C	
Generalisability	B	One study in children with type 1 diabetes and two studies in adults (both with type 1 and type 2 diabetes).
Applicability	A	One Australian study (in children). The adult studies were in Germany and the United States.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	
Recommendation		
There was insufficient evidence to make a recommendation.		

CHQ, Child Health Questionnaire

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9.2

Question 9.2 – children and adolescents: (i) metabolic outcomes

Q9.2		What is the effectiveness of education and/or psychological support programs in type 1 diabetes?
Evidence statement	There is some evidence from Level I and II studies for a beneficial effect of psychological support programs and education on glycaemic control in children and adolescents. There is insufficient evidence to identify a particular intervention that is more effective than standard care to improve glycaemic control.	
Evidence base	C	Two Level I studies with a low risk of bias. HbA _{1c} – Level II studies – 25 with a high risk of bias, 5 with a moderate risk of bias and 3 with a low risk of bias. Severe hypoglycaemia – Level II studies – 3 with a high risk of bias and 3 with a low risk of bias. Diabetic ketoacidosis – Level II studies – 2 with a moderate risk of bias.
Consistency	D	HbA _{1c} (meta-analysis – 0.5% difference in HbA _{1c} – significant heterogeneity) – findings inconsistent. Severe hypoglycaemia and diabetic ketoacidosis – findings inconsistent.
Clinical impact	C	
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9.2 (ii) – children: psychological outcomes

Q9.2		What is the effectiveness of education and/or psychological support programs in type 1 diabetes?
Evidence statement	There is Level I and II evidence that educational or psychological interventions improve some psychological outcomes, including psychological distress and self-management behaviours in young people with type 1 diabetes.	
Evidence base	A	Two Level I studies of low risk of bias (most studies of low or moderate risk of bias) and three Level II studies (one of moderate risk of bias and two of low risk of bias).
Consistency	D	(Couch et al 2008) Knowledge – inconsistent (5/11 significant difference). Self-management behaviour – inconsistent (6/15 significant effect, 4/15 positive effect not significant, 5/15 not significant). Psychosocial – inconsistent (7/15 significant effect). QoL – inconsistent (1/2 positive effect). (Winkley et al 2006) Psychological interventions – significant effect on psychological distress. Level II studies. QoL – significant improvement in one study, no effect in two studies.
Clinical impact	D	The findings are unlikely to alter current clinical practice.
Generalisability	B	Exclusions were not reported.
Applicability	A	One study was conducted in Australia, the others in countries with a well-established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	

QoL, quality of life

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9.2 (i) – adults: education and psychological interventions on metabolic outcomes

Q9.2		What is the effectiveness of education and/or psychological support programs in type 1 diabetes?
Evidence statement		The evidence base shows that the intensified education programs delivered in Reichard et al (1996) and the DAFNE Study Group (2002) are associated with reductions in HbA _{1c} compared with usual care. However, the intensified education programs delivered in the BITES program and by Terent et al (1985) were not associated with reductions in HbA _{1c} compared with usual care.
Evidence base	B	One Level I study with a low risk of bias (including two Level II studies with a high risk of bias), and two Level II studies with a low risk of bias.
Consistency	B	<ul style="list-style-type: none"> • HbA_{1c} –Results from the Level I study were inconsistent. In the larger study with a long intervention involving phone calls, etc, and a long follow-up, the intervention had a significant effect in combination with intensification of therapy. In the smaller study that was of poor quality and involved a relatively brief intervention, there was no effect. The Level II studies found a significant effect in one study but not in the other. • Severe hypoglycaemia was not reported (NA). • Diabetic ketacidosis was reported in one study, which showed no effect (NA).
Clinical impact	B/ C	HbA _{1c} – B Psychological outcomes – C
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were in countries with an established health-care system.
Other factors		The heterogeneity of interventions contributed to differences in findings. The focus here is on the incremental benefit associated with intensified education compared to standard education. However, issues around how to define standard education may affect interpretation. It is taken as given that education is an effective and critical component of care.
Details		For full systematic review, see Chapter 9 of the accompanying technical report

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 9.2 (ii) – adults: psychological outcomes

Q9.2		What is the effectiveness of education and/or psychological support programs in type 1 diabetes?
Evidence statement	There is Level II evidence that educational and psychological interventions improve some psychological outcomes (including psychological wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression) in adults.	
Evidence base	B	One Level I study with a low risk of bias (most included studies were of moderate and high risk of bias) and three Level II studies (two with a low risk of bias and one of moderate risk of bias).
Consistency	C	<ul style="list-style-type: none"> Educational interventions and psychological outcomes – both Level II studies reported a significant effect in terms of dietary freedom, quality of life, diabetes empowerment and treatment satisfaction (B). Psychological outcomes – the meta-analysis found no significant effect on psychological distress; of the Level II studies, one found a significant effect on wellbeing, diabetes-related distress, self-care behaviours, distress, anxiety and depression; the other two studies found no significant effect on psychological outcomes.
Clinical impact	D	The findings are unlikely alter current clinical practice.
Generalisability	B	Reported exclusions included pregnancy, non-English speaking, mental illness and diabetes complications.
Applicability	A	The studies were conducted in countries with an established health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 9 of the accompanying technical report	
Recommendation		
R9.2	Education and psychological support are an essential component of standard diabetes care. Intensified education and psychological support programs should be considered when treatment goals are not being met (Grade B).	

HbA_{1c}, glycated haemoglobin

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 10.1

Q10.1	What is the efficacy and safety of following a meal plan with a fixed carbohydrate intake versus a liberalised intake of dietary carbohydrate and/or matching insulin to estimated carbohydrate in type 1 diabetes?	
Evidence statement	Level II evidence (from three studies) shows that the use of insulin-to-carbohydrate ratios in multiple daily injection therapy reduces HbA _{1c} but has no clinically significant effect on weight, QoL or severe hypoglycaemia.	
Evidence base	C	Three Level II studies – one with a low risk of bias and two with a high risk of bias.
Consistency	C	HbA _{1c} – two studies were positive; 1% with the DAFNE Study Group (2002), 0.4% with Scavone et al (2010) (one study of high quality), and one study was negative (small sample size and high risk of bias).
	A	BMI/weight – no change in this outcome in two studies.
	D	QoL – reported in two studies, one showing a positive change and the other study (small sample size and high bias) showing no significant change.
	NA	Severe hypoglycaemic episodes – reported in one study.
Clinical impact	C	HbA _{1c} .
	D	BMI/weight.
	C	QoL.
	D	Severe hypoglycaemic episodes.
Generalisability	C	Studies included adults only, and excluded people with non-English speaking, psychiatric illness, pregnancy, complications and hypoglycaemia unawareness. The studies did not include children or the elderly, and may have included dietary naive subjects.
Applicability	B	Studies were conducted in Canada, Italy and the United Kingdom.
Other factors	None identified.	
Details	For full systematic review, see Chapter 10 of the accompanying technical report	
Recommendation		
R10.1	Matching of meal-time insulin dose to carbohydrate intake should be considered for patients using multiple daily injection therapy (Grade C).	

BMI, body mass index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 10.2

Q10.2		What is the efficacy and safety of low glycaemic index/high-fibre diets in type 1 diabetes?
Evidence statement	Level I evidence shows that a low GI diet has a beneficial effect on glycaemic control in adults and children. There is insufficient evidence to determine the effect of low-GI diets on body mass index, weight, severe hypoglycaemia or QoL in children, adolescents or adults with type 1 diabetes.	
Evidence base	A	One Level I study with a low risk of bias, comprising four Level II studies – one with a low risk of bias, one with a moderate risk of bias, and two with a high risk of bias. The rating is based on the Level I study, not the individual studies within it.
Consistency	A	HbA _{1c} – only reported in two studies, which together showed a pooled improvement of 0.5%.
	N/A	BMI – not reported in the systematic review.
	N/A	Weight – not reported in the systematic review.
	N/A	QoL – none of the studies used a validated tool.
	N/A	Severe hypoglycaemic episodes – not reported in the systematic review.
Clinical impact	C	For outcome of HbA _{1c} .
Generalisability	C	Evidence based on studies in children aged 8–13 years and adults; no studies included children aged under 8 years or those with complications. The studies from 1988 and 1992 are not relevant to current practice, because different regimens are now used.
Applicability	A	Studies were performed in countries with well-established health-care systems, including one Australian study.
Other factors	None identified.	
Details	For full systematic review, see Chapter 10 of the accompanying technical report	
Recommendation		
R10.2	Individuals with type 1 diabetes should be educated on low-GI diets (Grade A).	

BMI, body mass index; GI, glycaemic index; HbA_{1c}, glycated haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 10.3

Q10.3		What are the efficacy and safety of a high-protein diet in type 1 diabetes?
Evidence statement	There is insufficient evidence to determine the effect of modifying protein intake in individuals with type 1 diabetes.	
Evidence base	NA	
Consistency	NA	
Clinical impact	NA	
Generalisability	NA	
Applicability	NA	
Other factors	NA	
Details	For full systematic review, see Chapter 10 of the accompanying technical report	
Recommendation		
	There was insufficient evidence to make a recommendation.	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 10.4

Q10.4 What are the efficacy and safety of a high monounsaturated fat diet in type 1 diabetes?	
Evidence statement	Level II evidence (from one, good-quality study, small sample size) shows that, in nonobese adults with well-controlled, uncomplicated type 1 diabetes, a diet high in monounsaturated fats can have a beneficial effect on LDL-cholesterol, triglycerides, VLDL-triglycerides and VLDL-cholesterol. There is insufficient evidence to determine any effect on weight, body mass index, quality of life and severe hypoglycaemia of diets high in monounsaturated fat in children, adolescents or adults with type 1 diabetes
Evidence base	C Four Level II studies – one of low quality, two of moderate quality and one of high quality.
Consistency	A HbA _{1c} – all studies found no between-group differences.
	C Weight and BMI – one study found a significant increase in favour of intervention; all other studies found a nonsignificant difference.
	NR QoL – not reported.
	NR Severe hypoglycaemic episodes – not reported.
	D Results for lipids were variable – two studies showed no difference in lipids; one study (in adolescents) showed a significant increase in HDL in the comparator group and an inverse correlation between total cholesterol and LDL-cholesterol and dietary monounsaturated fat content in both groups; another study (in adults) showed a significant decrease in LDL in the intervention group.
Clinical impact	D Slight or restricted impact for outcomes of HbA _{1c} , weight and BMI, and lipids.
Generalisability	C The study groups was small (n=108 total), and participants found it difficult to follow the diet due to its difference from most western-style diets. The studies only included adults and adolescents.
Applicability	B Studies were performed in countries with well-established health-care systems, and included one Australian study.
Other factors	None identified.
Details	For full systematic review, see Chapter 10 of the accompanying technical report
Recommendation	
R10.4	Diets high in monounsaturated fats should not be used routinely in type 1 diabetes (Grade C).

BMI, body mass index; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; QoL, quality of life; RCT, randomised controlled trial; VLDL, very low density lipoprotein

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 12.1

Question 12.1 – complementary and alternative medicines: adverse effects

Q12.1	Complementary and alternative medicines and outcome/population adverse effects	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.	
Evidence base	C	One systematic review, of poor quality; eight Level II studies (seven with a low risk of bias; one with a high risk of bias).
Consistency	C	Five Level II studies (four with a low risk of bias; one with a high risk of bias) reported no adverse events. The systematic review reported that 6 of 291 patients treated with nicotinamide experienced an adverse effect. One study reported seven adverse events in the intervention (vitamin E) group, but this group was not statistically different from the other groups, and the adverse events were not considered serious. One study reported one adverse event (n=72; cinnamon intervention). One study reported one adverse event (n=82; vitamin E intervention).
Clinical impact	D	Interventions unlikely to be used in clinical practice.
Generalisability	A	Two studies were in adults – one study (fig leaf) reported no adverse events; one study (vitamin E) reported seven adverse events, but no statistically significant difference between groups. Four studies were in adolescents – two studies reported no adverse events; one study (cinnamon) reported one adverse event; one study (vitamin E) reported one adverse event. One study was in children (antioxidants) and reported no adverse events. One study was in children and adults (vitamin E + nicotinamide), and reported no adverse events.
Applicability	A	One study was conducted in Australia, five studies were in Europe and two were in the United States.
Other factors	None of the studies were powered to address adverse events.	
Details	For full systematic review, see Chapter 12 of the accompanying technical report	

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 12.1– complementary and alternative medicines: glycaemic control

Q12.1 Complementary and alternative medicines and outcome/population – glycaemic control combined	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.
Evidence base	C One systematic review of poor quality and 10 Level II studies (8 with a moderate risk of bias and 2 with a high risk of bias).
Consistency	A Studies were consistent. All included studies found no difference in HbA _{1c} (cinnamon, vitamin E + nicotinamide, vitamin E, alpha-lipoic acid, antioxidants, folate, vitamin D + nicotinamide, vitamin E + nicotinamide, fig leaf, and nicotinamide). Systematic review/meta-analysis (nicotinamide) showed no difference between intervention and control.
Clinical impact	D Results of studies unlikely to influence current clinical practice.
Generalisability	B Seven studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, nicotinamide, folate, and vitamin E). One study in children and adolescents (vitamin E + nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). A systematic review: age range 10–26 (nicotinamide).
Applicability	A One Australian study, two studies from the United States, and seven European studies.
Other factors	None identified.
Details	For full systematic review, see Chapter 12 of the accompanying technical report

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 12.1 – complementary and alternative medicines: insulin dose

Q12.1 Complementary and alternative medicines and outcome/population insulin dose	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.
Evidence base	C One systematic review/meta-analysis of poor quality. Nine Level II studies, seven of low risk of bias, two of high risk of bias.
Consistency	B Systematic review (nicotinamide) and eight Level II studies (cinnamon, vitamin E+ nicotinamide, alpha-lipoic acid, antioxidants, vitamin D + nicotinamide, nicotinamide + vitamin E, fenugreek, and nicotinamide) showed no difference in insulin dose. One study (fig leaf) showed a decrease in insulin requirement, but the study was of poor quality and of high risk of bias.
Clinical impact	D Results of studies unlikely to influence current clinical practice.
Generalisability	A Systematic review (nicotinamide) – age range 10–26 years. Five studies in adolescents (cinnamon, alpha-lipoic acid, vitamin D + nicotinamide, vitamin E + nicotinamide, and nicotinamide). One study in children (antioxidants). One study in adults (fig leaf). One study in adolescents and adults (fenugreek). One study in children and adolescents (vitamin E + nicotinamide).
Applicability	A Six studies were conducted in Europe, two in the United States and one in India.
Other factors	None identified.
Details	For full systematic review, see Chapter 12 of the accompanying technical report

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 12.1 – complementary and alternative medicines: lipid targets

Q12.1 Complementary and alternative medicines and outcome/population – lipid targets	
Evidence statement	There is Level I evidence for a low rate of adverse events with nicotinamide, and Level II evidence for a low rate of adverse events with vitamin E and cinnamon. All studies showed no efficacy of complementary and alternative medicines in glycaemic control in type 1 diabetes. There is insufficient evidence to determine the efficacy of complementary and alternative medicines on lowering insulin dose in type 1 diabetes. There is insufficient evidence to determine an effect of complementary and alternative medicines on lipid levels in type 1 diabetes.
Evidence base	C Two Level II studies of low risk of bias.
Consistency	A Studies were consistent – both found no effect of the intervention (vitamin E) in lowering lipids.
Clinical impact	D Results of studies unlikely to influence current clinical practice.
Generalisability	C Both studies were in adults. Exclusion criteria were only reported in one study; they were hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg), creatinine level \geq 15 mg/L or positive microalbuminuria, total cholesterol >300 mg/dl or triglycerides >500 mg/dl, pregnancy, breast feeding, women of childbearing age without adequate contraception, recent or unstable cardiovascular or cerebrovascular disease.
Applicability	C Both studies were conducted in Belgium.
Other factors	None identified.
Details	For full systematic review, see Chapter 12 of the accompanying technical report
Recommendation	
R12.1	CAM should not be used in type 1 diabetes to target metabolic outcomes (Grade C).

BP, blood pressure

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 13.1

Q13.1	What is the effectiveness of preconception care in women with type 1 diabetes in improving maternal and fetal outcomes?	
Evidence statement	Level III evidence shows that preconception care is effective at reducing congenital malformations, perinatal mortality and HbA _{1c} levels in women with type 1 diabetes,	
Evidence base	C	One systematic review (included 16 cohort studies – 8 prospective and 8 retrospective) and 10 cohort studies. Level III and IV evidence with a moderate risk of bias.
Consistency	A	Studies were generally consistent in their findings, particularly in regard to the primary outcomes (congenital malformations, perinatal mortality and HbA _{1c}).
Clinical impact	A	Results expected to affect clinical management.
Generalisability	A	For females of childbearing age.
Applicability	A	No studies from Australia, but studies undertaken in countries with a well-established health system.
Other factors	Question is not suitable for study by RCT.	
Details	For full systematic review, see Chapter 13 of the accompanying technical report	
Recommendation		
R13.1	Females of childbearing age with type 1 diabetes should be aware of the need for pregnancy planning and receive preconception care (Grade B).	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 13.2

Q13.2	What is the effectiveness of blood glucose control during pregnancy in women with type 1 diabetes in achieving blood glucose targets and improving maternal and fetal outcomes?	
Evidence statement	During pregnancy in women with type 1 diabetes, there is some evidence of harm for fasting blood glucose targeted at 6.7–8.9 mmol/L, compared to below 6.7 mmol/L.	
Evidence base	D	One Level I study that included three RCTs of high risk of bias, due to unclear allocation concealment methods, lack of blinded outcome assessment and high risk of selective outcome reporting bias.
Consistency	NA	Only one study was available.
Clinical impact	C	
Generalisability	B	
Applicability	A	No studies from Australia, but the studies were undertaken in countries with a well-established health system
Other factors	None identified.	
Details	For full systematic review, see Chapter 13 of the accompanying technical report	
Recommendation		
	There was insufficient evidence to make a recommendation.	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 14.1 – HbA_{1c}

Q14.1	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on glycaemic control.	
Evidence base	D	Level 1 evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	A	HbA _{1c} – only two studies reported this outcome, and no difference was found in either study. No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 14 of the accompanying technical report	

HbA_{1c}, glycated haemoglobin; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 14.1 – lipids

Q14.1	What is the metabolic effect of hormonal versus nonhormonal contraceptives in women with type 1 diabetes?	
Evidence statement	The four RCTs included in this systematic review provided insufficient evidence to assess whether progesterone-only and combined oral contraceptives differ from nonhormonal contraceptives in their impact on lipid metabolism.	
Evidence base	D	Level 1 evidence comprising four RCTs, three of high risk of bias and one of moderate risk of bias.
Consistency	C	Lipids – results were conflicting; one study reported a significant increase and three studies reported changes that were not clinically meaningful (i.e. they were within the normal range). No safety outcomes were reported.
Clinical impact	D	Results of studies unlikely to influence current clinical practice.
Generalisability	D	Sample size was small (n=62), and studies were not recent.
Applicability	C	All studies were conducted in Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 14 of the accompanying technical report	
Recommendation		
	There was insufficient evidence to make a recommendation.	

RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 16.1

Question 16.1 (i) – predictive factors for hypoglycaemia

Q16.1 (i) What are the predictive factors for severe hypoglycaemia?	
Evidence statement	Level II evidence indicates that younger age, longer duration of diabetes and hypoglycaemia unawareness are associated with higher risk of severe hypoglycaemia.
Evidence base	<p>B</p> <p>Younger age is associated with increased risk (e.g. OR 2.2): four Level II studies and one Level IV study in children; one Level II study in older children.</p> <p>Longer duration is associated with increased risk: (e.g. IRR 5.3, RR 1.39/5 years), four Level II studies in children and two Level II studies in adults.</p> <p>Lower HbA_{1c}: (RR 1.2 per 1%), three Level II studies in children; one Level IV study in children showing no relationship; three Level II studies and one Level IV study in adults.</p> <p>Sex: one Level I study in males; one Level I study showing no effect and one Level I study in adults.</p> <p>Psychological disorder: (RR1.56), one Level II study in children.</p> <p>Decreased hypoglycaemic awareness: one Level II study in children (RR4.6), one Level II and one Level IV study in adults.</p> <p>Prior hypoglycaemia: (HR 1.98) one Level I study and one Level IV study in adults.</p>
Consistency	B Generally consistent.
Clinical impact	B
Generalisability	A Populations were mostly clearly defined as paediatric or adult.
Applicability	A Large Australian studies as well as American and European.
Other factors	None identified.
Details	For full systematic review, see Chapter 16 of the accompanying technical report

HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, rate ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 16.1 (ii) – incidence of hypoglycaemia

Q16.1 (ii) What is the effect of intensive diabetes management on the incidence of hypoglycaemia?	
Evidence statement	Level I evidence from studies published before 1997 (including the DCCT) shows that intensive management is associated with a higher risk of severe hypoglycaemia.
Evidence base	A Two Level I studies one with a low risk of bias and one with a moderate risk of bias.
Consistency	B Direction of effect is consistent, but magnitude of effect varies when the results from DCCT are excluded: OR of experiencing one or more severe hypoglycaemic episode, 2.99 changed to 1.59. Significant interaction between effect and HbA _{1c} .
Clinical impact	C Limitations regarding currency of evidence.
Generalisability	Intensity of control may not be replicable. All studies included adults or adolescents, with a mean age of 18–42 years across included studies. No studies in children.
	B Adults.
	C Children.
Applicability	C Studies in America, Europe and North America (DCCT). Management practices have changed, so current delivery of care may be different from that in the evidence base.
Other factors	None identified.
Details	For full systematic review, see Chapter 16 of the accompanying technical report
Recommendation	
R16.1	Risk factors for severe hypoglycaemia should be identified (Grade B).

DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 16.2

Q16.2 What are the acute effects of hypoglycaemia and hyperglycaemia on cognitive function?	
Evidence statement	<p>Level II evidence shows that acute hypoglycaemia causes a temporally related impairment in cognitive performance.</p> <p>Level III evidence shows that acute hyperglycaemia may cause cognitive impairment in children and adults. One Level II study shows that acute hyperglycaemia above 22 mmol/L in children is associated with a comparable impairment to acute hypoglycaemia (<3 mmol/L).</p>
Evidence base	<p>B/ C</p> <p>Three Level II studies of moderate risk of bias (n=289 adults, n=61 primary school aged children) and 27 Level II or III studies, predominately of moderate risk of bias (clamp studies) (n=398 adults, n=48 children aged >6 years).</p> <p>B for hypoglycaemia. C for hyperglycaemia.</p>
Consistency	<p>A/ C</p> <p>BG level below 3.9 mmol/L and above 15 mmol/L in adults has a negative impact on cognition. BG level below 3.0 mmol/L and above 22.2 mmol/L in children has a negative impact on cognition.</p> <p>In adults, a recent history of severe hypoglycaemia attenuates the effect of hypoglycaemia, and higher HbA_{1c} and greater exposure to BG levels above 15 mmol/L are associated with a greater level of impairment during hyperglycaemia.</p> <p>In children, higher HbA_{1c} and frequency of severe hypoglycaemia are associated with a degree of impairment at BG levels above 22.2 mmol/L.</p> <p>Effects of hyperglycaemia and hypoglycaemia were highly individualised.</p> <p>A for hypoglycaemia. C for hyperglycaemia.</p>
Clinical impact	<p>A/ C</p> <p>'Hyperglycaemia resulted in increased errors and slower responses when performing basic verbal and mathematical tasks, which are important to numerous daily functions, such as balancing cheque books, calculating insulin dosing, and school and work performance.' (Cox et al 2005)</p> <p>Individual scores indicated that performance declines by more than 1 SD during hypoglycaemia and hyperglycaemia for more than 20% of children (Gonder-Frederick et al 2009).</p> <p>Group scores – during hypoglycaemia and hyperglycaemia there was, on average, a 20% decrease in speed (Gonder-Frederick et al 2009).</p> <p>A for hypoglycaemia. C for hyperglycaemia.</p>
Generalisability	<p>B</p> <p>No studies in children younger than 6 years.</p> <p>Reported exclusions included diabetes duration of less than 1 year, inability to read English, psychiatric disorder, substance abuse and pregnancy.</p>
Applicability	<p>A</p> <p>One study was in Australia; the rest were from countries with a well-established health-care system.</p>
Other factors	N/A
Details	For full systematic review, see Chapter 16 of the accompanying technical report
Recommendation	
R16.2	Acute hypoglycaemia (Grade B) and hyperglycaemia (Grade C) should be minimised to maintain optimal cognitive performance.

BG, blood glucose; HbA_{1c}, glycated haemoglobin; SD, standard deviation

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 16.3

Q16.3 How can severe hypoglycaemia be prevented?	
Evidence statement	Level II and Level IV evidence shows that specific educational interventions (in particular, BGAT) reduce the rate of severe hypoglycaemia.
Evidence base	C Two Level II studies (1 with 12 months follow-up) with moderate risk of bias, and two Level IV studies; one with low risk of bias and one with high risk of bias.
Consistency	B Reduction of severe hypoglycemia –the 24-month and 12-month results from the same study were conflicting (no effect at 12 months and a significant effect at 24 months). This may be explained by length of follow-up and the overall effect being positive. The other Level II study found a significant effect compared to control. The two Level II studies were consistent in reporting significant improvement compared to baseline. (Different definitions of severe hypoglycaemia and reporting methods were used.)
Clinical impact	A Level II studies used a method not described in detail. Level IV studies used published BG awareness training methodology.
Generalisability	B Populations were representative with studies in adolescents and adults. Compliance of the populations may vary. Children were not represented.
Applicability	A Studies were set in Europe and North America.
Other factors	One study reported the cost of intervention per 100 patients at €1000, and the yearly socioeconomic cost for severe hypoglycaemia at €17 440. Issues regarding language. Cost effectiveness should be considered with regard to implementation.
Details	For full systematic review, see Chapter 16 of the accompanying technical report
Recommendation	
R16.3	Structured education specifically targeting prevention of severe hypoglycaemia should be provided (Grade B).

BG, blood glucose; BGAT, blood glucose awareness training

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 17.1

Q17.1	Does ketone monitoring prevent ketoacidosis or hospital admission?	
Evidence statement	Blood ketone measurement compared with urine ketone measurement, as part of a sick-day management plan, reduces the rate of emergency presentations and hospitalisations.	
Evidence base	B	One Level II study of low risk of bias.
Consistency	N/A	Blood ketone monitoring resulted in a significant reduction (about 50%) in the incidence of hospitalisation and emergency assessment.
Clinical impact	A	This is an important clinical procedure that is easy to do at home.
Generalisability	B	Participants aged 3–22 years, and population not defined in terms of ethnicity. Exclusions included 'known emotional problems' and recurrent episodes of DKA.
Applicability	A	The study was undertaken in the United States, which has a well-developed health-care system.
Other factors	None identified.	
Details	For full systematic review, see Chapter 17 of the accompanying technical report	
Recommendation		
R17.1	Blood ketone measurement should be available as part of a comprehensive sick-day management plan (Grade C).	

DKA, diabetic ketoacidosis

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable.

Question 18.1

Question 18.1 –macrovascular

Q18.1		What is the effect of intensive glycaemic management on macrovascular complications?
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of cardiovascular disease.	
Evidence base	A	Level I evidence – two systematic reviews of low risk of bias and the DCCT/EDIC studies (Level II/III).
Consistency	A	Any cardiovascular event – a statistically significant difference was observed in all studies.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years. The age in the two systematic reviews was 18–42 years.
Applicability	A	The studies were not conducted at sites in Australia (the DCCT/EDIC studies were in the United States), but did include some rural and remote centres.
Other factors	None identified.	
Details	For full systematic review, see Chapter 18 of the accompanying technical report	

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 18.1 – microvascular

Q18.1		What is the effect of intensive glycaemic management on microvascular complications?
Evidence statement	Intensive glycaemic control in adolescents and adults with type 1 diabetes reduces the risk of microvascular outcomes.	
Evidence base	B	One Level II study of low risk of bias (DCCT), plus the long-term follow-up of the DCCT cohort (EDIC).
Consistency	NA	Only one study.
Clinical impact	A	
Generalisability	B	The DCCT was a large trial (n=1441). Children were not included in the DCCT; the age at baseline was 13–39 years.
Applicability	A	The studies were conducted in the United States, but did include some rural and remote centres.
Other factors	Intensive management in the DCCT referred to intensive glycaemic management, through a package of methods including MDI or CSII, frequent insulin dose adjustment, blood glucose monitoring at least four times per day and a weekly 3-am BG level, formal diabetes education, medical nutrition therapy, and physical activity advice. Such a package is not necessarily available at all centres in Australia. The incremental cost per life year gained was US\$28 661, but this is not necessarily informative for the Australian setting (see Chapter 4 of the guidelines on costs of diabetes).	
Details	For full systematic review, see Chapter 18 of the accompanying technical report	
Recommendation		
R18.1	Intensive glycaemic control should be implemented to reduce the risk of onset or progression of microvascular and development of macrovascular diabetes complications (Grade B).	

BG, blood glucose; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MDI, multiple daily injections

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 18.2

(i) Blood pressure control

Q18.2 (i)	How effective are antihypertensives at reducing blood pressure in type 1 diabetes?	
Evidence statement	Level II evidence shows that antihypertensive agents are effective at lowering blood pressure.	
Evidence base	B	Three RCTs, two of high risk of bias and one of low risk of bias.
Consistency	A	The studies were consistent in magnitude and direction.
Clinical impact	C	A 10 mmHg reduction in systolic pressure and a 5 mmHg reduction in diastolic pressure. The impact is most applicable to the adult population; this evidence has already been incorporated into clinical practice.
Generalisability	C	The studies had small sample sizes (n=16–35) and were in people with diabetes, with complications.
Applicability	B	All studies were conducted in northern Europe.
Other factors	None identified.	
Details	For full systematic review, see Chapter 18 of the accompanying technical report	

ACE, Angiotensin converting enzyme; RCT, randomised controlled trial

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

(ii) Complications

Question 18.2 (ii) – retinopathy

Q18.2 (ii)	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	Primary prevention: In normotensive patients with type 1 diabetes and no retinopathy, there is insufficient evidence to determine the effect of ACEI or ARB on the onset of retinopathy. Secondary prevention: In normotensive patients with type 1 diabetes and nonproliferative diabetic retinopathy, ACEI or ARB reduce the progression of retinopathy. Prespecified outcomes were two grades of retinopathy progression on the ETDRS scale (DIRECT and RASS) or one grade (EUCLID), thus with differing study outcome measures.	
Evidence base	B	Two Level II studies with combined low risk of bias.
Consistency	B	All studies were consistent in showing no effect on incidence of retinopathy. Evidence was conflicting about the progression of retinopathy. RASS: reduction with ACE (OR 0.35) and ARB (OR 0.3). DIRECT: No effect on predefined progression (2 steps), signify effect on post hoc analysis of three steps. No effect on proliferative retinopathy. EUCLID: Underpowered, and retinopathy not a primary outcome of this study.
Clinical impact	D	
Generalisability	B	Large, good or fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	B	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	None identified.	
Details	For full systematic review, see Chapter 18 of the accompanying technical report	

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio; RASS, Renin Angiotensin System Study

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 18.2 (ii) – nephropathy

Q18.2 (ii)	How effective are antihypertensives at reducing or preventing retinopathy, nephropathy, neuropathy and autonomic neuropathy?	
Evidence statement	<p>Primary prevention: In normotensive normoalbuminuric patients with type 1 diabetes, there is consistent evidence that neither ACEI nor ARB prevent the onset of microalbuminuria.</p> <p>Secondary prevention (progression): There is evidence that the use of ACEI prevents the progression from microalbuminuria to macroalbuminuria.</p> <p>There is evidence that ACEI attenuates or delays the progression from macroalbuminuria to doubling of creatinine or end-stage renal disease (combined death, dialysis and transplantation).</p>	
Evidence base	B	Primary.
	A	Secondary.
Consistency	B	Primary (results inconsistent for ACEI and ARB).
	A	Secondary – ACEI.
	B	Secondary – ARB.
Clinical impact	D	Primary.
	A	Secondary.
Generalisability	B	Large, good to fair-quality trials in normotensive, normoalbuminuric and microalbuminuric patients. All adult participants.
Applicability	A	Both large multicentre studies undertaken in Europe, the United Kingdom and the United States.
Other factors	Children and adolescents are not represented in the evidence base.	
Details	For full systematic review, see Chapter 18 of the accompanying technical report	
Recommendation		
R18.2	ACEI therapy should be used to prevent progression of diabetic nephropathy (Grade B)	

ACEI; angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OR, odds ratio

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 18.3

Q18.3 How effective are statins at correcting dyslipidaemia in type 1 diabetes?	
Evidence statement	Level I and II evidence demonstrates that statins are effective at reducing total and LDL cholesterol in adults with type 1 diabetes. Level I evidence demonstrates that statins reduce cardiovascular events in adults with type 1 diabetes.
Evidence base	A Level I study with inclusion criteria (>1000 patients) that ensure a low risk of bias. The Level II studies included four of low risk of bias, four of moderate risk of bias and two of high risk of bias.
Consistency	A LDL/total cholesterol –all studies show a statistically significant effect on lowering total cholesterol and LDL-cholesterol. Two studies showed a statistically significant increase in HDL, in contrast to the other studies.
	B HDL/triglycerides.
Clinical impact	A There was a large effect size and the finding has the potential to affect all patients with type 1 diabetes.
Generalisability	B Systematic review was large (n=1466 total). Numbers in individual studies were 8–82. Children and young adults were not represented in the evidence base.
Applicability	A Studies were conducted in Europe or the United States.
Other factors	PBS prescribing restrictions limit access to statins (e.g. microalbuminuria, Indigeneous). PBS guidelines use total cholesterol as the indicator, whereas paediatric guidelines recommend LDL cholesterol as the indication for therapy.
Details	For full systematic review, see Chapter 18 of the accompanying technical report
Recommendation	
R18.3	Statins are recommended for use in adults with type 1 diabetes, to reduce total and LDL cholesterol, and to reduce cardiovascular risk (Grade B).

HDL, high density lipoprotein; LDL, low density lipoprotein; PBS, Pharmaceutical Benefits Scheme

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 20.1

Q20.1 How often should individuals with type 1 diabetes be screened for coeliac disease?	
Evidence statement	There is an increased risk of coeliac disease in children and adolescents with type 1 diabetes compared to general population historical rates. The number of new cases detected 1 and 2 years after diagnosis is similar to the number of cases at diagnosis. The number of new cases detected after 10 years of diabetes duration is similar to the general population.
Evidence base	C Five Level II studies of moderate risk of bias, and two Level III studies of moderate risk of bias.
Consistency	B Prevalence of coeliac disease by duration was similar across the studies; it ranged from 1.6% to 8.1%. All studies demonstrated an increased risk of coeliac disease in type 1 diabetes. The direction of the effect was consistent, but the magnitude varied.
Clinical impact	B Detection of coeliac disease will have a major impact on patients.
Generalisability	B Most of the evidence is in children and adolescents. Only study in adults was a cross-sectional study not a longitudinal study.
Applicability	A
Other factors	None identified.
Details	For full systematic review, see Chapter 20 of the accompanying technical report
Recommendation	
R20.1	Screening for coeliac disease should occur at diagnosis of type 1 diabetes in children and adolescents; individuals with negative tests at diagnosis should be rescreened (Grade B).

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Question 20.2

Q20.2 How and how often should patients with type 1 diabetes be screened for thyroid disease?	
Evidence statement	Thyroid dysfunction is common in type 1 diabetes, and positive antibodies are strongly predictive of thyroid dysfunction.
Evidence base	C Five Level III studies with a moderate risk of bias, and one Level III study with a high risk of bias.
Consistency	B Consistent findings included the following: <ul style="list-style-type: none"> • A significant difference in the cumulative incidence of thyroid disease in patients positive to thyroid antibodies at diagnosis versus those negative to thyroid antibodies at diagnosis (four studies). • In studies measuring thyroid antibodies at multiple time-points, most patients were found to be positive at diagnosis of type 1 diabetes, rather than at follow-up testing (four studies). • Transient autoimmunity was not found in any patients who had highly positive thyroid antibody screen (>100 U/mL) (four studies). • Children and adults should be screened for thyroid disease and autoimmunity at diagnosis of type 1 diabetes (six studies). • Annual screening is suggested in antibody-positive patients, with less frequent screening in antibody negative patients (five studies).
Clinical impact	B Thyroid dysfunction is common in type 1 diabetes, and often requires treatment. Antibodies to TPO or TG are predictive of development of hypothyroidism.
Generalisability	A There is evidence in both children (n=1127) and adults (n=464) with type 1 diabetes. Follow-up was of 18 years' duration.
Applicability	A One study was conducted in a group of Australian children younger than 15 years; all other studies were undertaken in countries with a well-developed health-care system.
Other factors	N/A
Details	For full systematic review, see Chapter 20 of the accompanying technical report
Recommendation	
R20.2	Screening for thyroid dysfunction and testing for antibodies to thyroid peroxidase (TPO Ab) should be performed at diagnosis of type 1 diabetes; screening for thyroid dysfunction should be performed regularly thereafter (Grade B).

TG, thyroglobulin; TPO, thyroid peroxidase

Ratings: A, excellent; B, good; C, satisfactory; D, poor; NA, not applicable

Appendix D: Other resources

D1 Consumer reading materials

Publication details	Notes
<i>Children and adolescents</i>	
<i>Caring for diabetes in children and adolescents : a parent's manual</i> (Ambler and Cameron 2010) http://www.rch.org.au/diabetesmanual/index.cfm?doc_id=2352	A joint project of The Children's Hospital at Westmead and the Royal Children's Hospital. The resource takes into account (APEG (Australasian Paediatric Endocrine Group) 2005), and shows how these guidelines can be applied. The book will be useful to parents, grandparents, friends and other carers, as well as to young people with diabetes.
<i>Adults</i>	
<i>Straight to the point – a guide for adults living with type 1 diabetes</i> (Overland et al 2009b) http://www.jdrf.org.au/shop/products/Straight-to-the-Point.html	A useful resource for any adult living with type 1 diabetes, whether they are adjusting to life with the disease or are already familiar with living with it. The book covers everything from day-to-day management (including tips on food and exercise), to managing the disease at work and play, using real-life stories to illustrate the points made.
<i>A starter kit for recently diagnosed adult diabetes</i> (Reality Check 2005) www.realitycheck.org.au/starterkit/	A user friendly starter kit for adults with diabetes. With funding from the Federal Government's Department of Health and Ageing, a 40-page book for Adults who are newly-diagnosed with type 1 diabetes has been developed. The resource has been critically reviewed and endorsed for clinical accuracy by 30 diabetes-specialist health care professionals from around Australia. More than 250 diabetes centres and specialist practices are using the Kits to aid in education of their newly-diagnosed patients.
<i>Sick day management</i>	
<i>Guidelines for sick day management for people with type 1 diabetes</i> (ADEA 2006) http://www.adea.com.au/asset/view_document/979316048	This document has been produced in different versions for consumers and health-care professionals, and is currently under review.
<i>Nutrition therapy</i>	
<i>The new traffic light guide to food</i> (Diabetes Education and Assessment Programme 1997) http://catalogue.nla.gov.au/Record/2054756	A useful guide that will increase confidence about choosing foods and eating in a relaxed way.
<i>Continuous subcutaneous insulin infusion (CSII) pump therapy</i>	
<i>I'm considering an insulin pump</i> (Diabetes Australia VIC 2009) http://www.diabetesvic.org.au/type-1-diabetes/insulin-therapy-and-pumps/insulin-pump-information	A useful introduction for those considering an insulin pump and are just starting to find out about it as an option in therapy.
<i>Guidelines for continuous subcutaneous insulin infusion (CSII) pump therapy</i> (Victorian CSII Working Party 2009) http://www.diabetescrc.unimelb.edu.au/professionals/documents/CSIIguidelinesJuly2009-FINAL.pdf	A highly practical, advanced guide to insulin pump therapy.

D2 Health professional reading materials

Publication details	Organisation
Australian guidelines	
<i>Guidelines for the management of diabetic retinopathy</i> (Australian Diabetes Society 2008) http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di15.pdf	NHMRC Clinical care guideline, prepared by the Australian Diabetes Society
<i>Consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy</i> (McElduff et al 2005)	Australasian Diabetes in Pregnancy Society (ADIPS)
<i>Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus.</i> (Cheung et al 2009b)	The Australian Diabetes Society
International guidelines	
<i>Clinical practice consensus guidelines</i> (ISPAD 2009) http://www.ispad.org/FileCenter.html?CategoryID=5	International Society for Pediatric and Adolescent Diabetes (ISPAD)
<i>Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults</i> (NICE 2010) http://www.nice.org.uk/nicemedia/liver/10944/29390/29390.pdf	National Institute for Health and Clinical Excellence (NICE) (United Kingdom)
<i>Clinical guidelines for the management of type 1 diabetes in childhood and adolescence – currently under review</i> (ISPAD (International Society for Pediatric and Adolescent Diabetes) 2000) http://www.idf.org/node/1145?node=550	International Diabetes Federation (IDF)
<i>Standards of medical care in diabetes</i> (American Diabetes Association 2010)	American Diabetes Association (ADA)

Abbreviations and acronyms

A _{1c}	glycated haemoglobin
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADA	American Diabetes Association
ADC	Australian Diabetes Council
ADDQoL	audit of diabetes-dependent quality of life
ADEA	Australian Diabetes Educators Association
ADIPS	Australasian Diabetes in Pregnancy Society
ADS	Australian Diabetes Society
AER	albumin excretion rate
AHT	antihypertensive
AN	autonomic neuropathy
ANOVA	analysis of variation
APEG	Australasian Paediatric Endocrine Group
APS	autoimmune polyglandular syndrome
APS	Australian Psychological Society
ARA	antireticulin antibodies
ARB	angiotensin II receptor blocker
AUC	area under the glucose curve
BAI	Beck Anxiety Inventory
BASC	Behaviour Assessment System for Children
BDI	Beck Depression Inventory
BG	blood glucose

BGAT	blood glucose awareness training
BGL	blood glucose level
BMI	body mass index
BP	blood pressure
BRFSS	Behavioural Risk Factor Surveillance System
C	cholesterol
CACTI	coronary artery calcification in type 1 diabetes
CAN	cardiac autonomic neuropathy
CBGM	continuous blood glucose monitoring
CBCL	child behaviour check list
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CCF	congestive cardiac failure
CDI	Children's Depression Inventory
CFRD	cystic fibrosis related diabetes
CGM	continuous glucose monitoring
CGMS	continuous glucose monitoring systems
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CIMT	carotid intima-media thickness
CIPII	continuous intraperitoneal insulin infusion
CNS	central nervous system
CORE	Center for Outcomes Research

CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CT	conventional treatment
CVA	cardiovascular accident
CVD	cardiovascular disease
DA	Diabetes Australia
DAA	Dietitians Association of Australia
DAFNE	dose adjustment for normal eating
DARE	database of abstracts of reviews of effects
DCCT	Diabetes Control and Complications Trial
df	degrees of freedom
DIDMOAD	diabetes insipidus diabetes mellitus optic atrophy deafness
DIMD	Diagnostic Interview for Mental Disorders
DIS	Diagnostic Interview Schedule
DKA	diabetic ketoacidosis
DPT	Diabetes Prevention Trial
DQOL	diabetes quality of life
DSG	desogestrel
DSM	<i>Diagnostic and statistical manual of mental disorders</i>
E2	17 β -estradiol
EDE	Eating Disorders Examination
EDI	Eating Disorder Inventory
EDIC	Epidemiology of Diabetes Interventions and Complications
ED-NOS	eating disorders not otherwise specified
EDTRS	Early Treatment Diabetic Retinopathy Study

EE2	ethinyl-estradiol
ELISA	enzyme linked immunosorbent assay
EMA	antiendomysial antibodies
ENDIT	European Nicotinamide Diabetes Intervention Trial
EOD	early onset diabetes
ES	effect score
FBG	fasting blood glucose
FPG	fasting plasma glucose
FPIR	first phase insulin response
FSIQ	full scale intelligence quotient
GAD	glutamic acid decarboxylase
GADA	glutamic acid decarboxylase antibodies
GFR	glomerular filtration rate
GI	glycaemic index
GSD	gestodene
HADS	Hospital Anxiety and Depression Scale
HbA _{1c}	glycated haemoglobin
HDL	high density lipoprotein
HF	high frequency
HLA	human leukocyte antigen
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme
HNF	hepatic nuclear factor
HR	hazard ratio
HSCL	Hopkins Symptom Checklist
HRV	heart rate variability

HTA	health technology assessments
IA-2	insulinoma-associated 2 molecule
IAA	insulin autoantibodies
IAsp	insulin aspart
ICA	islet cell antigen
ICER	incremental cost-effectiveness ratio
IDDM	Insulin dependent diabetes mellitus
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
IIS	individual impairment score
IM	Intramuscular
INAHTA	International Network of Health Technology Assessment
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
ISCA	Interview Schedule for Children and Adolescents
IT	intensive treatment
ITT	intention to treat
IUD	intrauterine device
IV	intravenous
IVGTT	intravenous glucose tolerance test
JDFU	Juvenile Diabetes Foundation Unit
JDRF	Juvenile Diabetes Research Foundation
K6	Kessler 6 scale

LADA	latent autoimmune diabetes of the adult
LDL	low density lipoprotein
LF	low frequency
LNG	levonorgestrel
LOD	late onset diabetes
LY	life year
LYN	lynoestrenol
M-CIDI	Munchener Composite International Diagnostic Interview
MD	mean difference
MDI	multiple daily injections
MET	motivational enhancement therapy
MF	metformin
MHC	major histocompatibility complex
MI	myocardial infarction
MNSI	Michigan Neuropathy Screening Instrument
MODY	maturity onset diabetes in the young
mono	monounsaturated
MOS	Medical Outcomes Survey
MRDM	malnutrition related diabetes mellitus
mtDNA	mitochondrial DNA
NA	not available
NATA	National Association of Testing Authorities
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin dependent diabetes mellitus
NHMRC	National Health and Medical Research Council

NHS	National Health Service
NPH	neutral protamine Hagedorn
NR	not reported
NS	not significant
OR	odds ratio
OCP	oral contraceptive pill
PAID	Problem Areas in Diabetes program
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PGL	plasma glucose levels
PIQ	performance intelligence quotient
PL	placebo
poly	polyunsaturated
PPG	program project grant
PSE	present state examination
PTSD	post-traumatic stress disorder
OGTT	oral glucose tolerance test
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life years
QoL	quality of life
QUAL	qualitative
QUANT	quantitative
RACP	Royal Australian College of Physicians
RACGP	Royal Australian College of General Practitioners
RAS	renin-angiotensin system

RCFA	red cell fatty acids
RCMAS	Revised Children's Manifest Anxiety Scale
RCT	randomised controlled trial
RD	risk difference
ROC	receiver operating characteristic
RR	relative risk
S-ACE	serum angiotensin converting enzyme
SADS	Schedule for Affective Disorders and Schizophrenia
SADS-LA	Schedule for Affective Disorders and Schizophrenia Lifetime Version
SC	subcutaneous
SCL-90R	Symptom Checklist-90R
SD	standard deviation
SDS	standard deviation score
SE	standard error
SES	socioeconomic status
SH	severe hypoglycaemia
SI	Systeme International
SIMP	simplified
SMBG	self-monitoring of blood glucose
SPD	severe psychological distress
SPPC	self-perception profile for children
SR	systematic review
STAI	State-Trait Anxiety Inventory
TG	triglyceride
TPOA	thyroperoxidase antibodies

TRIGR	Trial to Prevent Type 1 Diabetes in the Genetically at Risk
TSH	thyroid stimulating hormone
tTG	anti-tissue transglutaminase
tTGA	anti-tissue transglutaminase antibody
UKPDS	United Kingdom Prospective Diabetes Study
VIQ	verbal intelligence quotient
VLDL	very low density lipoprotein
WHO	World Health Organization
WMD	weighted mean difference
YASR	Young Adult Self Report
YSR	Youth Self Report
ZnT-8	zinc transporter 8

References

- ACEI Trialist Group (ACE Inhibitors in Diabetic Nephropathy Trialist Group) (2001). Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data, *Annals of Internal Medicine*, **134**(5): 370–379.
- Ackard DM, Vik N, Neumark-Sztainer D, Schmitz KH, Hannan P and Jacobs DR, Jr. (2008). Disordered eating and body dissatisfaction in adolescents with type 1 diabetes and a population-based comparison sample: comparative prevalence and clinical implications, *Pediatric Diabetes*, **9**(4 Pt 1): 312–319.
- AddIT Research Group (Adolescent type 1 Diabetes Cardio-renal Intervention Trial Research Group) (2009). Adolescent type 1 Diabetes Cardio-renal Intervention Trial (AddIT), *British Medical Journal*, **9**: 79.
- ADEA (Australian Diabetes Educators Association) (2006). *Guidelines for sick day management for people with diabetes*, Canberra, Australian Diabetes Educators Association. Available at: http://www.adea.com.au/asset/view_document/979316048.
- Adolfsson P, Ornhaugen H and Jendle J (2009). Accuracy and reliability of continuous glucose monitoring in individuals with type 1 diabetes during recreational diving, *Diabetes Technology & Therapeutics*, **11**(8): 493–497.
- Ahmed N, Babaei-Jadidi R, Howell SK, Thornalley PJ and Beisswenger PJ (2005). Glycated and oxidized protein degradation products are indicators of fasting and postprandial hyperglycemia in diabetes, *Diabetes Care*, **28**(10): 2465–2471.
- Ahring KK, Ahring JP, Joyce C and Farid NR (1992). Telephone modem access improves diabetes control in those with insulin-requiring diabetes, *Diabetes Care*, **15**(8): 971–975.
- AiHW (Australian Institute of Health and Welfare) (2008). *Diabetes: Australian facts 2008*, Canberra, Australian Institute of Health and Welfare. Available at: <http://www.aihw.gov.au/publications/index.cfm/title/10394>.
- Akerblom HK (2010). The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study: recruitment, intervention and follow-up, *Diabetologia*.
- Allen C, LeCaire T, Palta M, Daniels K, Meredith M and D'Alessio DJ (2001). Risk factors for frequent and severe hypoglycemia in type 1 diabetes, *Diabetes Care*, **24**(11): 1878–1881.
- Allen KV and Frier BM (2003). Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention, *Endocrine Practice*, **9**(6): 530–543.
- Altschuler JA, Casella SJ, MacKenzie TA and Curtis KM (2007). The effect of cinnamon on A1C among adolescents with type 1 diabetes, *Diabetes Care*, **30**(4): 813–816.

- Ambler GR and Cameron FJ (Eds.) 2010. *Caring for diabetes in children and adolescents: a parent's manual*, The Children's Hospital at Westmead and the Royal Children's Hospital, Sydney.
- American Diabetes Association (2008). Nutrition recommendations and interventions for diabetes, *Diabetes Care*, **31**(Suppl 1): S61–S78.
- American Diabetes Association (2010). Standards of medical care in diabetes – 2010, *Diabetes Care*, **33**(Suppl 1): S11–61.
- Amsberg S, Anderbro T, Wredling R, Lisspers J, Lins PE, Adamson U and Johansson UB (2009). Experience from a behavioural medicine intervention among poorly controlled adult type 1 diabetes patients, *Diabetes Research & Clinical Practice*, **84**(1): 76–83.
- Anderbro T, Amsberg S, Adamson U, Bolinder J, Lins P, Wredling R, Moberg E, Lisspers J and Johansson UB (2010). Fear of hypoglycaemia in adults with Type 1 diabetes, *Diabetic Medicine*, **27**(10): 1151–1158.
- Andersen S, Tarnow L, Rossing P, Hansen BV and Parving HH (2000). Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy, *Kidney International*, **57**(2): 601–606.
- Andros V, Egger A and Dua U (2006). Blood pressure goal attainment according to JNC 7 guidelines and utilization of antihypertensive drug therapy in MCO patients with type 1 or type 2 diabetes, *Journal of Managed Care Pharmacy*, **12**(4): 303–309.
- Anonymous (1993). Implications of the Diabetes Control and Complications Trial. American Diabetes Association, *Diabetes Care*, **16**(11): 1517-1520.
- Anonymous (1995a). Adverse events and their association with treatment regimens in the diabetes control and complications trial, *Diabetes Care*, **18**(11): 1415–1427.
- Anonymous (1995b). Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial, *American Journal of Cardiology*, **75**(14): 894–903.
- Anonymous (1995c). The effect of intensive diabetes therapy on the development and progression of neuropathy, *Annals of Internal Medicine*, **122**(8): 561–568.
- Anonymous (1996). Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial, *Annals of Internal Medicine*, **124**(4): 379–388.
- Anonymous (1998a). Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial, *Archives of Ophthalmology*, **116**(7): 874–886.
- Anonymous (1998b). The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT), *Diabetologia*, **41**(4): 416–423.
- Anonymous (2005). Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia, *Diabetes Care*, **28**(5): 1245-1249.

- Anonymous (2006). Incidence and trends of childhood type 1 diabetes worldwide 1990–1999, *Diabetic Medicine*, **23**(8): 857–866.
- Anonymous (2011). Standards of medical care in diabetes – 2011, *Diabetes Care*, **34**(Suppl 1): S11–61.
- APEG (Australasian Paediatric Endocrine Group) (1996). *Australasian Paediatric Endocrine Group: APEG Handbook on Childhood and Adolescent Diabetes*, Sydney.
- APEG (Australasian Paediatric Endocrine Group) (2005). *Clinical Practice Guidelines: Type 1 diabetes in children and adolescents*. Available at: www.nhmrc.gov.au/publications.
- Armstrong DG, Todd WF, Lavery LA, Harkless LB and Bushman TR (1997). The natural history of acute Charcot's arthropathy in a diabetic foot specialty clinic, *Diabetic Medicine*, **14**(5): 357–363.
- Artz E, Warren-Ulanch J, Becker D, Greenspan S and Freemark M (2008). Seropositivity to celiac antigens in asymptomatic children with type 1 diabetes mellitus: association with weight, height, and bone mineralization, *Pediatric Diabetes*, **9**(4 Pt 1): 277–284.
- Australian Diabetes Society (1994). Position statement on scuba diving. Available at: <http://www.diabetessociety.com.au/position-statements.asp>.
- Australian Diabetes Society (2008). *Guidelines for the Management of Diabetic Retinopathy*. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/di15.pdf.
- Australian Government Department of Health and Ageing; NHMRC; New Zealand Ministry of Health (2006). *Nutrient reference values for Australia and New Zealand including recommended dietary intakes*, Canberra, NHMRC. Available at: <http://www.nhmrc.gov.au/publications/synopses/n35syn.htm>.
- Australian Institute of Health and Welfare (2009). Insulin-treated diabetes in Australia 2000–2007, *Diabetes series*, **11**(Cat. no. CVD 45).
- Austroroads (2006). *Assessing Fitness to Drive: Diabetes*. Available at: www.austroroads.com.au.
- Ayodele OE, Alebiosu CO and Salako BL (2004). Diabetic nephropathy – a review of the natural history, burden, risk factors and treatment, *Journal of the National Medical Association*, **96**(11): 1445–1454.
- Bagdade JD, Root RK and Bulger RJ (1974). Impaired leukocyte function in patients with poorly controlled diabetes, *Diabetes*, **23**(1): 9–15.
- Bailey R, Cooper JD, Zeitels L, Smyth DJ, Yang JH, Walker NM, Hypponen E, Dunger DB, Ramos-Lopez E, Badenhop K, et al. (2007). Association of the vitamin D metabolism gene CYP27B1 with type 1 diabetes, *Diabetes*, **56**(10): 2616–2621.
- Baillie R, Si D, Dowden M, O'Donoghue L, Connors C, Robinson G, Cunningham J and Weeramanthri T (2007). Improving organisational systems for diabetes care in Australian Indigenous communities, *BMC Health Services Research*, **7**: 67.

- Bain SC, Gill GV, Dyer PH, Jones AF, Murphy M, Jones KE, Smyth C and Barnett AH (2003). Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort), *Diabetic medicine*, **20**(10): 808–811.
- Baker IDI Heart and Diabetes Institute, The George Institute for Global Health and Adelaide Health Technology Assessment (2010). *National evidence-based guideline on prevention, identification and management of foot complications in diabetes (Part of the guidelines on management of type 2 diabetes mellitus)*, Melbourne, Baker IDI Heart & Diabetes Institute.
- Baker IDI Heart and Diabetes Institute, The George Institute for Global Health and Adelaide Health Technology Assessment (2011). *National evidence-based guideline on prevention, identification and management of foot complications in diabetes (Part of the guidelines on management of type 2 diabetes mellitus)*, Melbourne, Baker IDI Heart & Diabetes Institute.
- Baker WL, Gutierrez-Williams G, White CM, Kluger J and Coleman CI (2008). Effect of cinnamon on glucose control and lipid parameters, *Diabetes Care*, **31**(1): 41–43.
- Balasubramanyam A, Nalini R, Hampe CS and Maldonado M (2008). Syndromes of ketosis-prone diabetes mellitus, *Endocrine Reviews*, **29**(3): 292–302.
- Banerjee S, Tran K, Li H, Cimon K, Daneman D, Simpson SH and Campbell K (2007). *Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness*, Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH).
- Barera G, Bonfanti R, Viscardi M, Bazzigaluppi E, Calori G, Meschi F, Bianchi C and Chiumello G (2002). Occurrence of celiac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study, *Pediatrics*, **109**(5): 833–838.
- Barlow JH and Ellard DR (2006). The psychosocial well-being of children with chronic disease, their parents and siblings: an overview of the research evidence base, *Child: Care, Health & Development*, **32**(1): 19–31.
- Barnard K, Thomas S, Royle P, Noyes K and Waugh N (2010). Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review, *BMC Pediatrics*, **10**(50): doi: 10.1186/1471-2431-1110-1150.
- Barnard KD, Skinner TC and Peveler R (2006). The prevalence of co-morbid depression in adults with Type 1 diabetes: systematic literature review, *Diabetic Medicine*, **23**(4): 445–448.
- Barnett SJ, Shield JP, Potter MJ and Baum JD (1995). Foot pathology in insulin dependent diabetes, *Archives of Disease in Childhood*, **73**(2): 151–153.
- Barr EL, Wong TY, Tapp RJ, Harper CA, Zimmet PZ, Atkins R and Shaw JE (2006). Is peripheral neuropathy associated with retinopathy and albuminuria in individuals with impaired glucose metabolism? The 1999–2000 AusDiab, *Diabetes Care*, **29**(5): 1114–1116.

- Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, et al. (2009). Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes, *Nature Genetics*, **41**(6): 703–707.
- Bartley PC, Bogoev M, Larsen J and Philotheou A (2008). Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: A 2-year, randomized, controlled trial, *Diabetic Medicine*, **25**(4): 442–449.
- Batch JA and Werther GA (1992). Changes in growth hormone concentrations during puberty in adolescents with insulin dependent diabetes, *Clinical Endocrinology*, **36**(4): 411–416.
- Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, et al. (2010). Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes, *New England Journal of Medicine*, **363**(4): 311–320.
- Biermann E, Dietrich W, Rihl J and Standl E (2002). Are there time and cost savings by using telemanagement for patients on intensified insulin therapy? A randomised, controlled trial, *Computer Methods & Programs in Biomedicine*, **69**(2): 137–146.
- Biermann E, Dietrich W and Standl E (2000). Telecare of diabetic patients with intensified insulin therapy. A randomized clinical trial, *Studies in Health Technology & Informatics*, **77**: 327-332.
- Biesenbach G, Stoger H and Zazgornik J (1992). Influence of pregnancy on progression of diabetic nephropathy and subsequent requirement of renal replacement therapy in female type I diabetic patients with impaired renal function, *Nephrology Dialysis Transplantation*, **7**: 105–109.
- Bilous R, Chaturvedi N, Sjølie AK, Fuller J, Klein R, Orchard T, Porta M and Parving HH (2009). Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials, *Annals of Internal Medicine*, **151**(1): 11–20.
- Blanchard JF, Dean H, Anderson K, Wajda A, Ludwig S and Depew N (1997). Incidence and prevalence of diabetes in children aged 0-14 years in Manitoba, Canada, 1985-1993, *Diabetes Care*, **20**(4): 512-515.
- Blum RW, Garell D, Hodgman CH, Jorissen TW, Okinow NA, Orr DP and Slap GB (1993). Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine, *Journal of Adolescent Health*, **14**(7): 570–576.
- Bode B, Weinstein R, Bell D, McGill J, Nadeau D, Raskin P, Davidson J, Henry R, Huang WC and Reinhardt RR (2002). Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes, *Diabetes Care*, **25**(3): 439–444.
- Bogdanovic R (2008). Diabetic nephropathy in children and adolescents, *Pediatric Nephrology*, **23**(4): 507–525.

- Bognetti E, Riva MC, Bonfanti R, Meschi F, Viscardi M and Chiumello G (1998). Growth changes in children and adolescents with short-term diabetes, *Diabetes Care*, **21**(8): 1226–1229.
- Bolli GB, Kerr D, Thomas R, Torlone E, Sola-Gazagnes A, Vitacolonna E, Selam JL and Home PD (2009). Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study.[Erratum appears in *Diabetes Care*. 2009 Oct;32(10):1944], *Diabetes Care*, **32**(7): 1170–1176.
- Bonomo M, Cairoli R, Verde G, Morelli L, Moreo A, Grottaglie MD, Brambilla MC, Meneghini E, Aghemo P, Corigliano G, et al. (2009). Safety of recreational scuba diving in type 1 diabetic patients: the Deep Monitoring programme, *Diabetes & Metabolism*, **35**(2): 101–107.
- Boulot P, Chabbert-Buffet N, d'Ercole C, Floriot M, Fontaine P, Fournier A, Gillet JY, Gin H, Grandperret-Vauthier S, Geudj AM, et al. (2003). French multicentric survey of outcome of pregnancy in women with pregestational diabetes, *Diabetes Care*, **26**(11): 2990–2993.
- Boulton AJ (2008). The diabetic foot: grand overview, epidemiology and pathogenesis, *Diabetes/Metabolism Research and Reviews*, **24**(Suppl 1): S3–6.
- Brands AM, Biessels GJ, de Haan EH, Kappelle LJ and Kessels RP (2005). The effects of type 1 diabetes on cognitive performance: a meta-analysis, *Diabetes Care*, **28**(3): 726–735.
- Brink S, Laffel L, Likitmaskul S, Liu L, Maguire AM, Olsen B, Silink M and Hanas R (2009). Sick day management in children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 146–153.
- Brixner DI and McAdam-Marx C (2008). Cost-effectiveness of insulin analogs, *American Journal of Managed Care*, **14**(11): 766–775.
- Broers S, van Vliet KP, le Cessie S, Spinhoven P, van der Ven NC and Radder JK (2005). Blood glucose awareness training in Dutch type 1 diabetes patients: one-year follow-up, *Netherlands Journal of Medicine*, **63**(5): 164–169.
- Brown RJ, Wijewickrama RC, Harlan DM and Rother KI (2011). Uncoupling intensive insulin therapy from weight gain and hypoglycemia in type 1 diabetes, *Diabetes Technology & Therapeutics*, **13**(4): 457–460.
- Bruno G, Pinach S, Martini S, Cassader M, Pagano G and Guidetti CS (2003). Prevalence of type 1 diabetes-related autoantibodies in adults with celiac disease, *Diabetes Care*, **26**(5): 1644–1645.
- Bry L, Chen PC and Sacks DB (2001). Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin, *Clinical Chemistry*, **47**(2): 153–163.
- Bui H and Daneman D (2006). Type 1 diabetes in childhood, *Medicine*, **34**(3): 113–117.
- Bulsara MK, Holman CD, Davis EA and Jones TW (2004). The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes, *Diabetes Care*, **27**(10): 2293–2298.

- Bulsara MK, Holman CD, van Bockxmeer FM, Davis EA, Gallego PH and Beilby JP (2007). The relationship between ACE genotype and risk of severe hypoglycaemia in a large population-based cohort of children and adolescents with type 1 diabetes, *Diabetologia*, **50**(5): 965–971.
- Bussau VA, Ferreira LD, Jones TW and Fournier PA (2007). A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes, *Diabetologia*, **50**(9): 1815–1818.
- Buyken AE, Toeller M, Heitkamp G, Karamanos B, Rottiers R, Muggeo M and Fuller JH (2001). Glycemic index in the diet of European outpatients with type 1 diabetes: relations to glycosylated hemoglobin and serum lipids, *American Journal of Clinical Nutrition*, **73**(3): 574–581.
- Buyken AE, Toeller M, Heitkamp G, Vitelli F, Stehle P, Scherbaum WA and EURODIAB IDDM Complications Study Group (1998). Relation of fibre intake to HbA1c and the prevalence of severe ketoacidosis and severe hypoglycaemia, *Diabetologia*, **41**(8): 882–890.
- Cabrera-Rode E, Molina G, Arranz C, Vera M, Gonzalez P, Suarez R, Prieto M, Padron S, Leon R, Tillan J, et al. (2006). Effect of standard nicotinamide in the prevention of type 1 diabetes in first degree relatives of persons with type 1 diabetes, *Autoimmunity*, **39**(4): 333–340.
- Cameron CG and Bennett HA (2009). Cost-effectiveness of insulin analogues for diabetes mellitus, *Canadian Medical Association Journal*, **180**(4): 400–407.
- Cameron FJ, Clarke C, Hesketh K, White EL, Boyce DF, Dalton VL, Cross J, Brown M, Thies NH, Pallas G, et al. (2002). Regional and urban Victorian diabetic youth: clinical and quality-of-life outcomes, *Journal of Paediatrics & Child Health*, **38**(6): 593–596.
- Cameron FJ, Smidts D, Hesketh K, Wake M and Northam EA (2003). Early detection of emotional and behavioural problems in children with diabetes: the validity of the Child Health Questionnaire as a screening instrument, *Diabetic Medicine*, **20**(8): 646–650.
- Campbell S, Suebwongpat A, Standfield L and Weston A (2008). Systematic review update and economic evaluation for the New Zealand setting: Subcutaneous insulin pump therapy, *HSAC Report*, **1**(3).
- Canadian Diabetes Association (2008). Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, *Canadian Journal of Diabetes*, **32**(Suppl 1): S1–201.
- Carney CE, Ulmer C, Edinger JD, Krystal AD and Knauss F (2009). Assessing depression symptoms in those with insomnia: an examination of the beck depression inventory second edition (BDI-II), *Journal of Psychiatric Research*, **43**(5): 576–582.
- Catanzariti L, Faulks K, Moon L, Waters AM, Flack J and Craig ME (2009). Australia's national trends in the incidence of Type 1 diabetes in 0–14-year-olds, 2000–2006, *Diabetic Medicine*, **26**(6): 596–601.

- CDC Diabetes Cost-effectiveness Group (2002). Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes, *Journal of the American Medical Association*, **287**(19): 2542–2551.
- Cerutti F, Chiarelli F, Lorini R, Meschi F and Sacchetti C (2004). Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes, *Diabetes Care*, **27**(6): 1294–1298.
- Chang J, Rayner CK, Jones KL and Horowitz M Diabetic gastroparesis-backwards and forwards, *Journal of Gastroenterology and Hepatology*, **26**(Suppl 1): 46–57.
- Channon SJ, Huws-Thomas MV, Rollnick S, Hood K, Cannings-John RL, Rogers C and Gregory JW (2007). A multicenter randomized controlled trial of motivational interviewing in teenagers with diabetes, *Diabetes Care*, **30**(6): 1390–1395.
- Chase HP (2005). A randomized multicenter trial comparing the glucoWatch biographer with standard glucose monitoring in children with type 1 diabetes, *Diabetes Care*, **28**(5): 1101–1106.
- Chase HP, Arslanian S, White NH and Tamborlane WV (2008). Insulin glargine versus intermediate-acting insulin as the basal component of multiple daily injection regimens for adolescents with type 1 diabetes mellitus, *Journal of Pediatrics*, **153**(4): 547–553.
- Chase HP, Crews KR, Garg S, Crews MJ, Cruickshanks KJ, Klingensmith G, Gay E and Hamman RF (1992). Outpatient management vs in-hospital management of children with new-onset diabetes, *Clinical Pediatrics*, **31**(8): 450–456.
- Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R and Garg SK (2001). Continuous subcutaneous glucose monitoring in children with type 1 diabetes, *Pediatrics*, **107**(2): 222–226.
- Chase HP, Roberts MD, Wightman C, Klingensmith G, Garg SK, Van Wyhe M, Desai S, Harper W, Lopatin M, Bartkowiak M, et al. (2003). Use of the GlucoWatch biographer in children with type 1 diabetes, *Pediatrics*, **111**(4 Pt 1): 790–794.
- Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG and Davies MJ (2007). Glargine versus NPH insulin: Efficacy in comparison with insulin aspart in a basal bolus regimen in type 1 diabetes-The glargine and aspart study (GLASS). A randomised cross-over study, *Research and Clinical Practice*, **77**(2): 215–222.
- Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, Bilous R, Sjølie AK and DIRECT Programme Study Group (2008). Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials, *Lancet*, **372**(9647): 1394–1402.
- Chaturvedi N, Sjølie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, Rogulja-Pepeonik Z and Fuller JH (1998). Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus, *Lancet*, **351**(9095): 28–31.

- Chaturvedi N, Stephenson JM and Fuller JH (1995). The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study, *Diabetes Care*, **18**(6): 785–792.
- Chetty VT, Almulla A, Oduyungbo A and Thabane L (2008). The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: a systematic review, *Diabetes Research & Clinical Practice*, **81**(1): 79–87.
- Cheung N, Donaghue KC, Liew G, Rogers SL, Wang JJ, Lim SW, Jenkins AJ, Hsu W, LiLee M and Wong TY (2009a). Quantitative assessment of early diabetic retinopathy using fractal analysis, *Diabetes Care*, **32**(1): 106–110.
- Cheung N, Rogers SL, Donaghue KC, Jenkins AJ, Tikellis G and Wong TY (2008). Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes, *Diabetes Care*, **31**(9): 1842–1846.
- Cheung NW, Conn JJ, d'Emden MC, Gunton JE, Jenkins AJ, Ross GP, Sinha AK, Andrikopoulos S, Colagiuri S and Twigg SM (2009b). Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus, *Medical Journal of Australia*, **191**(6): 339–344.
- Chico A, Vidal-Rios P, Subira M and Novials A (2003). The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control, *Diabetes Care*, **26**(4): 1153–1157.
- Cho YH, Couper JJ and Donaghue KC (2010). Complications of childhood diabetes and the role of technology, *Pediatric Endocrinology Reviews*, (Suppl 3): 422–431.
- Cho YH, Craig ME, Hing S, Gallego PH, Poon M, Chan A and Donaghue KC (2011). Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006, *Pediatric Diabetes*.
- Clar C, Waugh N and Thomas S (2007). Routine hospital admission versus out-patient or home care in children at diagnosis of type 1 diabetes mellitus, *Cochrane Database of Systematic Reviews*, (2): CD004099.
- Clarke SL, Craig ME, Garnett SP, Chan AK, Cowell CT, Cusumano JM, Kordonouri O, Sambasivan A and Donaghue KC (2006). Increased adiposity at diagnosis in younger children with type 1 diabetes does not persist, *Diabetes Care*, **29**(7): 1651–1653.
- Clarke W, Jones T, Rewers A, Dunger D and Klingensmith GJ (2009). Assessment and management of hypoglycemia in children and adolescents with diabetes, *Pediatric Diabetes*, **10** Suppl 12: 134-145.
- Clifford A, Jackson Pulver L, Richmond R, Shakeshaft A and Ivers R (2009). Disseminating best-evidence health-care to Indigenous health-care settings and programs in Australia: identifying the gaps, *Health Promot Int*, **24**(4): 404-415.

- Cohen N, Minshall ME, Sharon-Nash L, Zakrzewska K, Valentine WJ and Palmer AJ (2007). Continuous subcutaneous insulin infusion versus multiple daily injections of insulin: economic comparison in adult and adolescent type 1 diabetes mellitus in Australia, *Pharmacoeconomics*, **25**(10): 881–897.
- Colagiuri S, Brnabic A, Gomez M, Fitzgerald B, Buckley A and Colagiuri R (2009). *DiabCoSt Australia : Type 1: assessing the burden of type 1 diabetes in Australia*, Diabetes Australia, Canberra.
- Collier A, Steedman DJ, Patrick AW, Nimmo GR, Matthews DM, MacIntyre CC, Little K and Clarke BF (1987). Comparison of intravenous glucagon and dextrose in treatment of severe hypoglycemia in an accident and emergency department, *Diabetes Care*, **10**(6): 712–715.
- Collier GR, Giudici S, Kalmusky J, Wolever TM, Helman G, Wesson V, Ehrlich RM and Jenkins DJ (1988). Low glycemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children, *Diabetes Nutrition and Metabolism*, **1**: 11–19.
- Colton PA, Olmsted MP, Daneman D, Rydall AC and Rodin GM (2007). Five-year prevalence and persistence of disturbed eating behavior and eating disorders in girls with type 1 diabetes, *Diabetes Care*, **30**(11): 2861–2862.
- Concannon P, Chen WM, Julier C, Morahan G, Akolkar B, Erlich HA, Hilner JE, Nerup J, Nierras C, Pociot F, et al. (2009). Genome-wide scan for linkage to type 1 diabetes in 2,496 multiplex families from the Type 1 Diabetes Genetics Consortium, *Diabetes*, **58**(4): 1018–1022.
- Conway B, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW and Orchard TJ (2010). Temporal patterns in overweight and obesity in Type 1 diabetes, *Diabetic Medicine*, **27**(4): 398-404.
- Cook J, Daneman D, Spino M, Sochett E, Perlman K and Balfe JW (1990). Angiotensin converting enzyme inhibitor therapy to decrease microalbuminuria in normotensive children with insulin-dependent diabetes mellitus, *Journal of Pediatrics*, **117**(1Pt1): 39–45.
- Cooper-Dehoff RM, Egelund EF and Pepine CJ (2011). Blood pressure lowering in patients with diabetes-one level might not fit all, *Nature Reviews Cardiology*, **8**(1): 42–49.
- Corriveau EA, Durso PJ, Kaufman ED, Skipper BJ, Laskaratos LA and Heintzman KB (2008). Effect of Carelink, an internet-based insulin pump monitoring system, on glycemic control in rural and urban children with type 1 diabetes mellitus, *Pediatric Diabetes*, **9**(4 Pt 2): 360–366.
- Cosson E, Hamo-Tchatchouang E, Dufaitre-Patouraux L, Attali JR, Paries J and Schaepeelynck-Belicar P (2009). Multicentre, randomised, controlled study of the impact of continuous sub-cutaneous glucose monitoring (GlucoDay) on glycaemic control in type 1 and type 2 diabetes patients, *Diabetes & Metabolism*, **35**(4): 312–318.
- Couch R, Jetha M, Dryden DM, Hooten N, Liang Y, Durec T, Sumamo E, Spooner C, Milne A, O'Gorman K, et al. (2008). Diabetes education for children with type 1 diabetes mellitus and their families, *Evidence Report/Technology Assessment*, **166**: 1–144.

- Couper JJ, Beresford S, Hirte C, Baghurst PA, Pollard A, Tait BD, Harrison LC and Colman PG (2009). Weight gain in early life predicts risk of islet autoimmunity in children with a first-degree relative with type 1 diabetes, *Diabetes Care*, **32**(1): 94–99.
- Court JM, Cameron FJ, Berg-Kelly K and Swift PG (2009). Diabetes in adolescence, *Pediatric Diabetes*, **10**(Suppl 12): 185–194.
- Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B and Clarke W (2001). Blood glucose awareness training (BGAT-2): long-term benefits, *Diabetes Care*, **24**(4): 637–642.
- Cox DJ, Gonder-Frederick L, Ritterband L, Patel K, Schachinger H, Fehm-Wolfsdorf G, Hermanns N, Snoek F, Zrebiec J, Polonsky W, et al. (2006). Blood glucose awareness training: What is it, where is it, and where is it going?, *Diabetes Spectrum*, **19**(1): 43–49.
- Cox DJ, Gonder-Frederick LA, Kovatchev BP, Young-Hyman DL, Donner TW, Julian DM and Clarke WL (1999). Biopsychobehavioral model of severe hypoglycemia. II. Understanding the risk of severe hypoglycemia, *Diabetes Care*, **22**(12): 2018–2025.
- Cox DJ, Kovatchev BP, Gonder-Frederick LA, Summers KH, McCall A, Grimm KJ and Clarke WL (2005). Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes, *Diabetes Care*, **28**(1): 71–77.
- Craig ME, Duffin AC, Gallego PH, Lam A, Cusumano J, Hing S and Donaghue KC (2008). Plantar fascia thickness, a measure of tissue glycation, predicts the development of complications in adolescents with type 1 diabetes, *Diabetes Care*, **31**(6): 1201–1206.
- Craig ME, Femia G, Broyda V, Lloyd M and Howard NJ (2007). Type 2 diabetes in Indigenous and non-Indigenous children and adolescents in New South Wales, *Medical Journal of Australia*, **186**(10): 497–499.
- Craig ME, Hattersley A and Donaghue KC (2009a). Definition, epidemiology and classification of diabetes in children and adolescents, *Pediatric Diabetes*, **10**(Suppl 12): 3–12.
- Craig ME, Twigg SM, Donaghue KC, Cheung NW, Cameron FJ, Conn J, Jenkins AJ, Silink M and Group ATDGEA (2011). *Draft national evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults*, Canberra, Australian Government Dept of Health and Ageing.
- Craig ME, Wong CH, Alexander J, Maguire AM and Silink M (2009b). Delayed referral of new-onset type 1 diabetes increases the risk of diabetic ketoacidosis, *Medical Journal of Australia*, **190**(4): 219.
- Crinò A, Schiaffini R, Manfrini S, Mesturino C, Visalli N, Beretta Anguissola G, Suraci C, Pitocco D, Spera S, Corbi S, et al. (2004). A randomized trial of nicotinamide and vitamin E in children with recent onset type 1 diabetes (IMDIAB IX), *European journal of endocrinology / European Federation of Endocrine Societies*, **5**: 719–724. Available at: RCT
- Crone J, Rami B, Huber WD, Granditsch G and Schober E (2003). Prevalence of celiac disease and follow-up of EMA in children and adolescents with type 1 diabetes mellitus, *Journal of Pediatric Gastroenterology & Nutrition*, **37**(1): 67–71.

- Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS and Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes, *New England Journal of Medicine*, **352**(24): 2477–2486.
- Cryer PE (2010). Hypoglycemia in type 1 diabetes mellitus, *Endocrinology & Metabolism Clinics of North America*, **39**(3): 641–654.
- Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ and Endocrine Society (2009). Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline, *Journal of Clinical Endocrinology & Metabolism*, **94**(3): 709–728.
- Cryer PE, Davis SN and Shamoon H (2003). Hypoglycemia in diabetes, *Diabetes Care*, **26**(6): 1902–1912.
- CTT Collaborators (Cholesterol Treatment Trialists' Collaborators), Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J and Baigent C (2008). Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, *Lancet*, **371**(9607): 117–125.
- D'Ambrogi E, Giurato L, D'Agostino MA, Giacomozzi C, Macellari V, Caselli A and Uccioli L (2003). Contribution of plantar fascia to the increased forefoot pressures in diabetic patients, *Diabetes Care*, **26**(5): 1525–1529.
- D'hooge R, Hellinckx T, Van Laethem C, Stegen S, De Schepper J, Van Aken S, Dewolf D and Calders P (2010). Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial, *Clinical Rehabilitation*, **Nov 26**.
- DAFNE Study Group (2002). Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial, *British Medical Journal*, **325**(7367): 746.
- Dahlquist G and Kallen B (2007). School performance in children with type 1 diabetes--a population-based register study, *Diabetologia*, **50**(5): 957–964.
- Danne T, Mortensen HB, Hougaard P, Lynggaard H, Aanstoot HJ and Chiarelli F (2001). Persistent differences among centers over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidovre Study Group, *Diabetes Care*, **24**(8): 1342–1347.
- Davis EA, Keating B, Byrne GC, Russell M and Jones TW (1998). Impact of improved glycaemic control on rates of hypoglycaemia in insulin dependent diabetes mellitus, *Archives of Disease in Childhood*, **78**(2): 111–115.
- Davis EA, Soong SA, Byrne GC and Jones TW (1996). Acute hyperglycaemia impairs cognitive function in children with IDDM, *Journal of Pediatric Endocrinology and Metabolism*, **9**(4): 455–461.
- Dawson SI, Willis J, Florkowski CM and Scott RS (2008). All-cause mortality in insulin-treated diabetic patients: a 20-year follow-up, *Diabetes Research & Clinical Practice*, **80**(1): e6-9.

- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1986). The diabetes control and complications trial (DCCT). Design and methodologic considerations for the feasibility phase, *Diabetes*, **35**(5): 530–545.
- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1991). Epidemiology of severe hypoglycemia in the diabetes control and complications trial, *American Journal of Medicine*, **90**(4): 450–459.
- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *New England Journal of Medicine*, **329**(14): 977–986.
- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1994). Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial, *Journal of Pediatrics*, **125**(2): 177–188.
- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1995). Resource Utilization and Costs of Care in the Diabetes Control and Complications Trial, *Diabetes Care*, **18**(11): 1468–1478.
- DCCT Research Group (Diabetes Control and Complications Trial Research Group) (1997). Hypoglycemia in the Diabetes Control and Complications Trial, *Diabetes Care*, **46**(2): 271–286.
- DCCT/EDIC Research Group (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group), Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, et al. (2007). Long-term effect of diabetes and its treatment on cognitive function. [Erratum appears in N Engl J Med. 2009 Nov 5;361(19):1914], *New England Journal of Medicine*, **356**(18): 1842–1852.
- de Leon EM, Jacober SJ, Sobel JD and Foxman B (2002). Prevalence and risk factors for vaginal *Candida* colonization in women with type 1 and type 2 diabetes, *BMC Infectious Diseases*, **2**(1): 1–6.
- de Vries R, Kerstens MN, Sluiter WJ, Groen AK, van Tol A, Dullaart RP and Dullaart RPF (2005). Cellular cholesterol efflux to plasma from moderately hypercholesterolaemic type 1 diabetic patients is enhanced, and is unaffected by simvastatin treatment, *Diabetologia*, **48**(6): 1105–1113.
- Dear Gde L, Pollock NW, Ugucioni DM, Dovenbarger J, Feinglos MN and Moon RE (2004). Plasma glucose responses in recreational divers with insulin-requiring diabetes, *Undersea & Hyperbaric Medicine*, **31**(3): 291–301.
- Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D and Phillip M (2006). Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring, *Diabetes Care*, **29**(12): 2730–2732.

- Deiss D, Hartmann R, Schmidt J and Kordonouri O (2006b). Results of a randomised controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CGMS) on glycaemic control in children and adolescents with type 1 diabetes, *Experimental & Clinical Endocrinology & Diabetes*, **114**(2): 63–67.
- Delamater AM (2009). Psychological care of children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 175–184.
- Demarini S, Mimouni F, Tsang RC, Khoury J and Hertzberg V (1994). Impact of metabolic control of diabetes during pregnancy on neonatal hypocalcemia: a randomized study, *Obstetrics & Gynecology*, **83**(6): 918–922.
- Department of Health and Ageing (2009). *Australian National Diabetes Information Audit & Benchmarking*, Canberra, ACT, Department of Health and Ageing.
- Department of Health Western Australia (2009). Health Networks Branch, Department of Health, Perth, Western Australia. Available at: http://www.healthnetworks.health.wa.gov.au/modelsofcare/docs/Paediatric_Chronic_Diseases_Transition_Framework.pdf.
- Diabetes Australia VIC (2009). *I'm considering an insulin pump. Information for people with type 1 diabetes*, Melbourne, Diabetes Australia VIC. Available at: http://www.diabetesvic.org.au/images/stories/PDF_files/representing%20connecting%20informing.pdf?phpMyAdmin=fsgZ8MzPBx-Okd83pnoO,vcNPM5.
- Diabetes Education and Assessment Programme (1997). *The new traffic light guide to food*, Diabetes Education and Assessment Programme (NSW), St Leonards, NSW.
- Donaghue KC, Chiarelli F, Trotta D, Allgrove J and Dahl-Jorgensen K (2009). Microvascular and macrovascular complications associated with diabetes in children and adolescents, *Pediatric Diabetes*, **10**(Suppl 12): 195–203.
- Donaghue KC, Kordonouri O, Chan A and Silink M (2003). Secular trends in growth in diabetes: are we winning?, *Archives of Disease in Childhood*, **88**(2): 151–154.
- Donaghue KC, Pena MM, Chan AK, Blades BL, King J, Storlien LH and Silink M (2000). Beneficial effects of increasing monounsaturated fat intake in adolescents with type 1 diabetes, *Diabetes Research & Clinical Practice*, **48**(3): 193–199.
- Doolan A, Donaghue K, Fairchild J, Wong M and Williams AJ (2005). Use of HLA typing in diagnosing celiac disease in patients with type 1 diabetes, *Diabetes Care*, **28**(4): 806–809.
- Dougherty G, Schiffrin A, White D, Soderstrom L and Sufrategui M (1999). Home-based management can achieve intensification cost-effectively in type I diabetes, *Pediatrics*, **103**(1): 122–128.
- Dovey-Pearce G, Hurrell R, May C, Walker C and Doherty Y (2005). Young adults' (16–25 years) suggestions for providing developmentally appropriate diabetes services: a qualitative study, *Health and Social Care in the Community*, **13**(5): 409–419.

- Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M and Tamborlane WV (2004). A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. , *Diabetes Care*, **27**(7): 1554–1558.
- DPT-1 Study Group (2002). Effects of insulin in relatives of patients with type 1 diabetes mellitus, *New England Journal of Medicine*, **346**(22): 1685–1691.
- Draelos MT, Jacobson AM, Weinger K, Widom B, Ryan CM, Finkelstein DM and Simonson DC (1995). Cognitive function in patients with insulin-dependent diabetes mellitus during hyperglycemia and hypoglycemia, *American Journal of Medicine*, **98**(2): 135–144.
- Dreyer M, Prager R, Robinson A, Busch K, Ellis G, Souhami E and Van Leendert R (2005). Efficacy and safety of insulin glulisine in patients with type 1 diabetes, *Hormone & Metabolic Research*, **37**(11): 702–707.
- Duffin AC, Kidd R, Chan A and Donaghue KC (2003). High plantar pressure and callus in diabetic adolescents. Incidence and treatment, *Journal of the American Podiatric Medical Association*, **93**(3): 214–220.
- Duffin AC, Lam A, Kidd R, Chan AK and Donaghue KC (2002). Ultrasonography of plantar soft tissues thickness in young people with diabetes, *Diabetic Medicine*, **19**(12): 1009–1013.
- Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TP, Glaser NS, Hanas R, Hintz RL, Levitsky LL, et al. (2004). European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents, *Pediatrics*, **113**(2): e133-140.
- Eastman RC, Leptien AD and Chase HP (2003). Cost-effectiveness of use of the GlucoWatch Biographer in children and adolescents with type 1 diabetes: a preliminary analysis based on a randomized controlled trial, *Pediatric Diabetes*, **4**(2): 82–86.
- Ebbehøj E, Poulsen PL, Hansen KW, Knudsen ST, Mølgaard H and Mogensen CE (2002). Effects on heart rate variability of metoprolol supplementary to ongoing ACE-inhibitor treatment in Type I diabetic patients with abnormal albuminuria, *Diabetologia*, **45**(7): 965–975.
- Edge CJ, St Leger Dowse M and Bryson P (2005). Scuba diving with diabetes mellitus--the UK experience 1991–2001, *Undersea & Hyperbaric Medicine*, **32**(1): 27–37.
- Edidin DV (1985). Cutaneous manifestations of diabetes mellitus in children, *Pediatric Dermatology*, **2**(3): 161–179.
- Egger M, Davey Smith G, Stettler C and Diem P (1997a). Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis, *Diabetic Medicine*, **14**(11): 919–928.
- Egger M, Davey Smith G, Stettler C and Diem P (1997b). Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis., *Diabetic Medicine*, **14**(11): 919–928.

- Ekblom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Mølviig J and Mathiesen ER (2001). Pregnancy outcome in type 1 diabetic women with microalbuminuria, *Diabetes Care*, **24**: 1739–1744.
- Elixhauser A, Weschler JM, Kitzmiller JL, Marks JS, Bennert HW, Jr., Coustan DR, Gabbe SG, Herman WH, Kaufmann RC, Ogata ES, et al. (1993). Cost-benefit analysis of preconception care for women with established diabetes mellitus, *Diabetes Care*, **16**(8): 1146-1157.
- Ely KA, Tse G, Simpson JF, Clarfled R and Page DL (2000). Diabetic mastopathy. A clinicopathologic review, *American Journal of Clinical Pathology*, **113**(4): 541–545.
- Endocrinology Expert Group (2009). *Endocrinology*, Therapeutic Guidelines Ltd, Melbourne, Vic., Australia.
- Engelen W, Manuel YKB, Vertommen J, De Leeuw I and Van Gaal L (2005). Effects of micronized fenofibrate and vitamin E on in vitro oxidation of lipoproteins in patients with type 1 diabetes mellitus, *Diabetes & Metabolism*, (2): 197–204.
- Fanelli CG, Pampanelli S, Porcellati F, Bartocc L, Scionti L, Rossetti P and Bolli GB (2003). Rate of fall of blood glucose and physiological responses of counterregulatory hormones, clinical symptoms and cognitive function to hypoglycaemia in Type I diabetes mellitus in the postprandial state, *Diabetologia*, **36**(1): 53–64.
- Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S and Cryer PE (1998). Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes, *Diabetes*, **47**(12): 1920–1927.
- Farrag OA (1987). Prospective study of 3 metabolic regimens in pregnant diabetics, *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **27**(1): 6–9.
- Farrar D, Tuffnell DJ and West J (2007). Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes, *Cochrane Database of Systematic Reviews*, (3): CD005542.
- Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC and Montori VM (2009). Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections, *Journal of Clinical Endocrinology & Metabolism*, **94**(3): 729–740.
- Fenton CL, Clemons PM and Francis GL (1999). How do the results of the diabetes control and complications trial relate to the practice of pediatrics: who should have intensive management?, *Pediatric Annals*, **28**(9): 600–604.
- Fiallo-Scharer R and Diabetes Research in Children Network Study Group (2005). Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes, *Journal of Clinical Endocrinology & Metabolism*, **90**(6): 3387–3391.
- Field MJ (Ed.) 1996. *Telemedicine – A guide to assessing telecommunications in health care*, National Academy Press, Washington, DC.

- Fontvieille AM, Rizkalla SW, Penforinis A, Acosta M, Bornet FR and Slama G (1992). The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks, *Diabetic Medicine*, **9**(5): 444–450.
- Foster DW and McGarry JD (1983). The metabolic derangements and treatment of diabetic ketoacidosis, *New England Journal of Medicine*, **309**(3): 159–169.
- Fourlanos S, Varney MD, Tait BD, Morahan G, Honeyman MC, Colman PG and Harrison LC (2008). The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes, *Diabetes Care*, **31**(8): 1546–1549.
- Fox LA, Buckloh LM, Smith SD, Wysocki T and Mauras N (2005). A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. , *Diabetes Care* **28**: 1277–1281.
- Frank M (1996). Factors associated with non-compliance with a medical follow-up regiment after discharge from a pediatric diabetes clinic, *Canadian Journal of Diabetes Care*, **20**: 13–20.
- Fried LF, Forrest KY, Ellis D, Chang Y, Silvers N and Orchard TJ (2001). Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes, *Journal of Diabetes & its Complications*, **15**(3): 113–119.
- Friedman S, Vila G, Timsit J, Boitard C and Mouren-Simeoni M (1998). Anxiety and depressive disorders in an adult insulin-dependent diabetic mellitus (IDDM) population: Relationships with glycaemic control and somatic complications, *European Psychiatry*, **13**(6): 295–302.
- Fuchtenbusch M, Rabl W, Grassl B, Bachmann W, Standl E and Ziegler AG (1998). Delay of type I diabetes in high risk, first degree relatives by parenteral antigen administration: the Schwabing Insulin Prophylaxis Pilot Trial, *Diabetologia*, **41**(5): 536–541.
- Gale EA, Bingley PJ, Emmett CL, Collier T and European Nicotinamide Diabetes Intervention Trial G (2004). European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes, *Lancet*, **363**(9413): 925–931.
- Gaudieri PA, Chen R, Greer TF and Holmes CS (2008). Cognitive function in children with type 1 diabetes: a meta-analysis, *Diabetes Care*, **31**(9): 1892–1897.
- Gendelman N, Snell-Bergeon JK, McFann K, Kinney G, Paul Wadwa R, Bishop F, Rewers M and Maahs DM (2009). Prevalence and correlates of depression in individuals with and without type 1 diabetes, *Diabetes Care*, **32**(4): 575–579.
- George JT, Valdovinos AP, Russell I, Dromgoole P, Lomax S, Torgerson DJ, Wells T and Thow JC (2008). Clinical effectiveness of a brief educational intervention in Type 1 diabetes: results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial, *Diabetic Medicine*, **25**(12): 1447–1453.

- George JT, Valdovinos AP, Thow JC, Russell I, Dromgoole P, Lomax S, Torgerson DJ and Wells T (2007). Brief intervention in type 1 diabetes - Education for self-efficacy (BITES): Protocol for a randomised control trial to assess biophysical and psychological effectiveness, *BMC Endocrine Disorders*, **7**(6).
- Georgopoulos A, Bantle JP, Noutsou M and Hoover HA (2000). A high carbohydrate versus a high monounsaturated fatty acid diet lowers the atherogenic potential of big VLDL particles in patients with type 1 diabetes, *Journal of Nutrition*, **130**(10): 2503–2507.
- Gerds E, Svarstad E, Aanderud S, Myking OL, Lund-Johansen P and Omvik P (1998). Factors influencing reduction in blood pressure and left ventricular mass in hypertensive type-1 diabetic patients using captopril or doxazosin for 6 months, *American Journal of Hypertension*, **11**(10): 1178–1187.
- Giacco R, Parillo M, Rivellese AA, Lasorella G, Giacco A, D'Episcopo L and Riccardi G (2000). Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in type 1 diabetic patients, *Diabetes Care*, **23**(10): 1461–1466.
- Giannini C, Lombardo F, Currò F, Pomilio M, Bucciarelli T, Chiarelli F and Mohn A (2007). Effects of high-dose vitamin E supplementation on oxidative stress and microalbuminuria in young adult patients with childhood onset type 1 diabetes mellitus, *Diabetes/Metabolism Research and Reviews*, (7): 539–546.
- Gilbert K and Millard R (2006). 'Perceived and actual information needs of adults at diagnosis with type 1 diabetes', *International Diabetes Federation World Diabetes Congress*, Cape Town, South Africa.
- Gilbertson HR, Brand-Miller JC, Thorburn AW, Evans S, Chondros P and Werther GA (2001). The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes, *Diabetes Care*, **24**(7): 1137–1143.
- Gilbertson HR, Thorburn AW, Brand-Miller JC, Chondros P and Werther GA (2003). Effect of low-glycemic-index dietary advice on dietary quality and food choice in children with type 1 diabetes, *American Journal of Clinical Nutrition*, **77**(1): 83–90.
- Glastras SJ, Craig ME, Verge CF, Chan AK, Cusumano JM and Donaghue KC (2005). The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications, *Diabetes Care*, **28**(9): 2170–2175.
- Gold AE, MacLeod KM, Deary IJ and Frier BM (1995). Hypoglycemia-induced cognitive dysfunction in diabetes mellitus: Effect of hypoglycemia unawareness, *Physiology and Behavior*, **58**(3): 501–511.
- Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N and Karp M (1986). Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study, *American Journal of Obstetrics & Gynecology*, **155**(2): 293–297.
- Golicki DT, Golicka D, Groele L and Pankowska E (2008). Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis, *Diabetologia*, **51**(2): 233–240.

- Gonder-Frederick LA, Cox DJ, Driesen NR, Ryan CM and Clarke WL (1994). Individual differences in neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM, *Diabetes*, **43**(12): 1407–1412.
- Gonder-Frederick LA, Zrebiec J, Bauchowitz A, Lee J, Cox D and Ritterband L (2008). Detection of hypoglycemia by children with type 1 diabetes 6 to 11 years of age and their parents: a field study, *Pediatrics*, **121**(3): e489–495.
- Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU, Ritterband LM, Magee JC, Cox DJ and Clarke WL (2009). Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study, *Diabetes Care*, **32**(6): 1001–1006.
- Goss PW, Paterson MA and Renalson J (2010). A 'radical' new rural model for pediatric diabetes care, *Pediatric Diabetes*, **11**(5): 296–304.
- Goyder EC, Spiers N, McNally PG, Drucquer M and Botha JL (1999). Do diabetes clinic attendees stay out of hospital? A matched case-control study, *Diabetic Medicine*, **16**(8): 687–691.
- Grey M, Boland EA, Davidson M, Li J and Tamborlane WV (2000). Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life, *Journal of Pediatrics*, **137**(1): 107–113.
- Grey M, Whittemore R, Jaser S, Ambrosino J, Lindemann E, Liberti L, Northrup V and Dziura J (2009). Effects of coping skills training in school-age children with type 1 diabetes, *Research in Nursing & Health*, **32**(4): 405–418.
- Grigoryan OR, Grodnitskaya EE, Andreeva EN, Shestakova MV, Melnichenko GA and Dedov I (2006). Contraception in perimenopausal women with diabetes mellitus, *Gynecological Endocrinology*, **22**(4): 198–206.
- Grigsby AB, Anderson RJ, Freedland KE, Clouse RE and Lustman PJ (2002). Prevalence of anxiety in adults with diabetes: a systematic review, *Journal of Psychosomatic Research*, **53**(6): 1053–1060.
- Grima DT, Thompson MF and Sauriol L (2007). Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada, *Pharmacoeconomics*, **25**(3): 253–266.
- Gschwend MH, Aagren M and Valentine WJ (2009). Cost-effectiveness of insulin detemir compared with neutral protamine Hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in five European countries, *Journal of Medical Economics*, **12**(2): 114–123.
- Gschwend S, Ryan C, Atchison J, Arslanian S and Becker D (1995). Effects of acute hyperglycemia on mental efficiency and counterregulatory hormones in adolescents with insulin-dependent diabetes mellitus, *Journal of Pediatrics*, **126**(2): 178–184.
- Gulve EA and Spina RJ (1995). Effect of 7–10 days of cycle ergometer exercise on skeletal muscle GLUT-4 protein content, *Journal of Applied Physiology*, **79**(5): 1562–1566.

- Gunczler P and Lanes R (1999). Poor metabolic control decreases the growth velocity of diabetic children, *Diabetes Care*, **22**(6): 1012.
- Haller MJ, Atkinson MA and Schatz D (2005). Type 1 diabetes mellitus: etiology, presentation, and management, *Pediatric Clinics of North America*, **52**(6): 1553–1578.
- Hanas R, Donaghue KC, Klingensmith G and Swift PG (2009). ISPAD clinical practice consensus guidelines 2009 compendium. Introduction, *Pediatric Diabetes*, **10**(Suppl 12): 1–2.
- Hanas R and John G (2010). 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement, *Diabetes Care*, **33**(8): 1903-1904.
- Handelsman P, Craig ME, Donaghue KC, Chan A, Blades B, Laina R, Bradford D, Middlehurst A, Ambler G, Verge CF, et al. (2001). Homogeneity of metabolic control in New South Wales and the Australian Capital Territory, Australia, *Diabetes Care*, **24**(9): 1690–1691.
- Hansen D, Bennedbaek FN, Hoier-Madsen M, Hegedus L and Jacobsen BB (2003). A prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 diabetes, *European Journal of Endocrinology*, **148**(2): 245–251.
- Hansen MV, Pedersen-Bjergaard U, Heller SR, Wallace TM, Rasmussen AK, Jorgensen HV, Pramming S and Thorsteinsson B (2009). Frequency and motives of blood glucose self-monitoring in type 1 diabetes, *Diabetes Research & Clinical Practice*, **85**(2): 183–188.
- Harjutsalo V, Sjoberg L and Tuomilehto J (2008). Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study, *Lancet*, **371**(9626): 1777–1782.
- Harrison LC, Honeyman MC, Steele CE, Stone NL, Sarugeri E, Bonifacio E, Couper JJ and Colman PG (2004). Pancreatic beta-cell function and immune responses to insulin after administration of intranasal insulin to humans at risk for type 1 diabetes, *Diabetes Care*, **27**(10): 2348–2355.
- Hattersley A, Bruining J, Shield J, Njolstad P and Donaghue KC (2009). The diagnosis and management of monogenic diabetes in children and adolescents, *Pediatric Diabetes*, **10 Suppl 12**: 33-42.
- Haynes A, Bower C, Bulsara MK, Jones TW and Davis EA (2004). Continued increase in the incidence of childhood Type 1 diabetes in a population-based Australian sample (1985-2002), *Diabetologia*, **47**(5): 866-870.
- Helgeson VS, Snyder PR, Escobar O, Siminerio L and Becker D (2007). Comparison of adolescents with and without diabetes on indices of psychosocial functioning for three years, *Journal of Pediatric Psychology*, **32**(7): 794–806.
- Helgeson VS, Viccaro L, Becker D, Escobar O and Siminerio L (2006). Diet of adolescents with and without diabetes, *Diabetes Care*, **29**: 982–987.

- Heller S, Damm P, Mersebach H, Skjoth TV, Kaaja R, Hod M, Duran-Garcia S, McCance D and Mathiesen ER (2010). Hypoglycemia in type 1 diabetic pregnancy: Role of preconception insulin aspart treatment in a randomized study, *Diabetes Care*, **33**(3): 473–477.
- Heller S, Koenen C and Bode B (2009). Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial, *Clinical Therapeutics*, **31**(10): 2086–2097.
- Herman WH, Janz NK, Becker MP and Charron-Prochownik D (1999). Diabetes and pregnancy. Preconception care, pregnancy outcomes, resource utilization and costs, *J Reprod Med*, **44**(1): 33–38.
- Hermanns N, Kulzer B, Gulde C, Eberle H, Pradler E, Patzelt-Bath A and Haak T (2009). Short-term effects on patient satisfaction of continuous glucose monitoring with the glucoday with real-time and retrospective access to glucose values: A crossover study, *Diabetes Technology & Therapeutics*, **11**(5): 275–281.
- Hermanns N, Kulzer B, Krichbaum M, Kubiak T and Haak T (2006). How to screen for depression and emotional problems in patients with diabetes: comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment, *Diabetologia*, **49**(3): 469–477.
- Herzer M and Hood KK (2010). Anxiety symptoms in adolescents with type 1 diabetes: association with blood glucose monitoring and glycemic control, *Journal of Pediatric Psychology*, **35**(4): 415–425.
- Hirai FE, Moss SE, Klein BE, Klein R, Hirai FE and Moss SE (2007). Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy, *Diabetes Care*, **30**(6): 1437–1441.
- Hirsch IB, Abelson J, Bode BW, Fischer JS, Kaufman FR, Mastrototaro J, Parkin CG, Wolpert HA and Buckingham BA (2008). Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study, *Diabetes Technology & Therapeutics*, **10**(5): 377–383.
- Hoffman RG, Speelman DJ, Hinnen DA, Conley KL, Guthrie RA and Knapp RK (1989). Changes in cortical functioning with acute hypoglycemia and hyperglycemia in type I diabetes, *Diabetes Care*, **12**(3): 193–197.
- Holl RW, Grabert M, Heinze E, Sorgo W and Debatin KM (1998). Age at onset and long-term metabolic control affect height in type-1 diabetes mellitus, *European Journal of Pediatrics*, **157**(12): 972–977.
- Holmes-Walker DJ, Llewellyn AC and Farrell K (2007). A transition care programme which improves diabetes control and reduces hospital admission rates in young adults with Type 1 diabetes aged 15-25 years, *Diabetic Medicine*, **24**(7): 764-769.
- Holmes CS, Hayford JT, Gonzalez JL and Weydert JA (1983). A survey of cognitive functioning at difference glucose levels in diabetic persons, *Diabetes Care*, **6**(2): 180–185.

- Holmes CS, Koepke KM and Thompson RG (1986). Simple versus complex performance impairments at three blood glucose levels, *Psychoneuroendocrinology*, **11**(3): 353–357.
- Holmes CS, Koepke KM, Thompson RG, Gyves PW and Weydert JA (1984). Verbal fluency and naming performance in type I diabetes at different blood glucose concentrations, *Diabetes Care*, **7**(5): 454–459.
- Hommel E, Andersen P, Gall MA, Nielsen F, Jensen B, Rossing P, Dyerberg J and Parving HH (1992). Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy, *Diabetologia*, **35**(5): 447–451.
- Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, Binder C and Parving HH (2003). Decreasing incidence of severe diabetic microangiopathy in type 1 diabetes, *Diabetes Care*, **26**: 1258–1264.
- Howard K, White S, Salkeld G, McDonald S, Craig JC, Chadban S and Cass A (2010). Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis, *Value Health*, **13**(2): 196–208.
- Huang EA and Gitelman SE (2008). The effect of oral alpha-lipoic acid on oxidative stress in adolescents with type 1 diabetes mellitus, *Pediatric Diabetes*, **9**(3 Pt 2): 69–73.
- Ismail K, Maissi E, Thomas S, Chalder T, Schmidt U, Bartlett J, Patel A, Dickens C, Creed F and Treasure J (2010). A randomised controlled trial of cognitive behaviour therapy and motivational interviewing for people with type 1 diabetes mellitus with persistent sub-optimal glycaemic control: A diabetes and psychological therapies (ADaPT) study, *Health Technology Assessment*, **14**(22): 1–127.
- ISPAD (International Society for Pediatric and Adolescent Diabetes) (2000). *Clinical guidelines for the management of type 1 diabetes mellitus in childhood and adolescence*, International Diabetes Federation. Available at: <http://www.idf.org/node/1145?node=550>.
- ISPAD (International Society for Pediatric and Adolescent Diabetes) (2009). *ISPAD Clinical Practice Consensus Guidelines 2009*, ISPAD. Available at: <http://www.ispad.org/FileCenter.html?CategoryID=5>.
- Jacobsen AM, Hauser ST, Willett J, Woldsdorf JI and Herman L (1997). Consequences of irregular versus continuous medical follow-up in children and adolescents with insulin-dependent diabetes mellitus, *Journal of Pediatrics*, **131**: 727–733.
- Jacobsen IB, Henriksen JE and Beck-Nielsen H (2009). The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control, *Basic & Clinical Pharmacology & Toxicology*, **105**(3): 145–149.
- Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M and Dahms W (2007). Long-term effect of diabetes and its treatment on cognitive function, *New England Journal of Medicine*, **356**(18): 1842–1852.
- Jandeleit-Dahm K and Cooper ME (2002). Hypertension and diabetes, *Current Opinion in Nephrology & Hypertension*, **11**(2): 221–228.

- JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group) (2009). The effect of continuous glucose monitoring in well-controlled type 1 diabetes, *Diabetes Care*, **32**(8): 1378–1383.
- JDRF CGM Study Group (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group), Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, et al. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes, *New England Journal of Medicine*, **359**(14): 1464–1476.
- Jones GR, Barker G, Goodall I, Schneider H, Shephard MD and Twigg SM (2011). Position Statement - Change of HbA1c Reporting to the new SI units, *Medical Journal of Australia*, **195**(1): 45-46.
- Jones TW and Davis EA (2003). Hypoglycemia in children with type 1 diabetes: current issues and controversies., *Pediatric Diabetes*, **4**(3): 143–150.
- Kaaja R (2009). Vascular complications in diabetic pregnancy, *Thrombosis Research*, **123**(Suppl 2): S1–3.
- Kaila B and Taback SP (2001). The effect of day care exposure on the risk of developing type 1 diabetes: a meta-analysis of case-control studies, *Diabetes Care*, **24**(8): 1353–1358.
- Kalergis M, Pacaud D, Strychar I, Meltzer S, Jones PJH and Yale JF (2000). Optimizing insulin delivery: Assessment of three strategies in intensive diabetes management, *Diabetes Obesity and Metabolism*, **2**(5): 299–305.
- Kanumakala S, Dabadghao P, Carlin JB, Vidmar S and Cameron FJ (2002). Linear growth and height outcomes in children with early onset type 1 diabetes mellitus – a 10-yr longitudinal study, *Pediatr Diabetes*, **3**: 189–193.
- Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V, Kanariou M and Karayianni C (2009). Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM), *Hormone Research*, **71**(4): 201–206.
- Kaspers S, Kordonouri O, Schober E, Grabert M, Hauffa BP, Holl RW and German Working Group for Pediatric D (2004). Anthropometry, metabolic control, and thyroid autoimmunity in type 1 diabetes with celiac disease: A multicenter survey, *Journal of Pediatrics*, **145**(6): 790–795.
- Kent S, Chen R, Kumar A and Holmes C (2009). Individual growth curve modeling of specific risk factors and memory in youth with type 1 diabetes: an accelerated longitudinal design, *Child Neuropsychology*, **16**(2): 169–181.
- Kessler RC, Green JG, Gruber MJ, Sampson NA, Bromet E, Cuitan M, Furukawa TA, Gureje O, Hinkov H, Hu CY, et al. (2010). Screening for serious mental illness in the general population with the K6 screening scale: results from the WHO World Mental Health (WMH) survey initiative, *International Journal of Methods in Psychiatric Research*, **19**(Suppl 1): 4–22.

- Khan AS, McLoughney CR and Ahmed AB (2006). The effect of metformin on blood glucose control in overweight patients with Type 1 diabetes, *Diabetic Medicine*, **23**(10): 1079–1084.
- Kilpatrick ES, Rigby AS, Goode K and Atkin SL (2007). Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes, *Diabetologia*, **50**(12): 2553–2561.
- Kipps S, Bahu T, Ong K, Ackland FM, Brown RS, Fox CT, Griffin NK, Knight AH, Mann NP, Neil HA, et al. (2002). Current methods of transfer of young people with Type 1 diabetes to adult services, *Diabetic Medicine*, **19**(8): 649–654.
- Kitabchi AE, Umpierrez GE, Murphy MB and Kreisberg RA (2006). Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association, *Diabetes Care*, **29**(12): 2739–2748.
- Kjaer K, Hangaard J, Petersen NE and Hagen C (1992). Effect of simvastatin in patients with type I (insulin-dependent) diabetes mellitus and hypercholesterolemia, *Acta Endocrinologica*, **126**(3): 229–232.
- Knip M, Virtanen SM, Seppa K, Ilonen J, Savilahti E, Vaarala O, Reunanen A, Teramo K, Hamalainen AM, Paronen J, et al. (2010). Dietary intervention in infancy and later signs of beta-cell autoimmunity, *New England Journal of Medicine*, **363**(20): 1900–1908.
- Komatsu WR, Gabbay MA, Castro ML, Saraiva GL, Chacra AR, de Barros Neto TL and Dib SA (2005). Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus, *Pediatr Diabetes*, **6**(3): 145–149.
- Kong MF and Horowitz M (1999). Gastric emptying in diabetes mellitus: relationship to blood-glucose control, *Clinics in Geriatric Medicine*, **15**(2): 321–338.
- Kordonouri O and Hartmann R (2005). Higher body weight is associated with earlier onset of Type 1 diabetes in children: confirming the 'Accelerator Hypothesis', *Diabetic Medicine*, **22**(12): 1783–1784.
- Kordonouri O, Hartmann R, Deiss D, Wilms M and Gruters-Kieslich A (2005). Natural course of autoimmune thyroiditis in type 1 diabetes: association with gender, age, diabetes duration, and puberty, *Archives of Disease in Childhood*, **90**(4): 411–414.
- Kordonouri O, Maguire AM, Knip M, Schober E, Lorini R, Holl RW and Donaghue KC (2009). Other complications and associated conditions with diabetes in children and adolescents, *Pediatric Diabetes*, **10**(Suppl 12): 204–210.
- Kordonouri O, Meyer K, Egerer K, Hartmann R, Scheffler S, Burmester GR, Kuckelkorn U, Danne T and Feist E (2004). Prevalence of 20S proteasome, anti-nuclear and thyroid antibodies in young patients at onset of type 1 diabetes mellitus and the risk of autoimmune thyroiditis, *Journal of Pediatric Endocrinology*, **17**(7): 975–981.
- Kovacs M, Goldston D, Obrosky DS and Bonar LK (1997). Psychiatric disorders in youths with IDDM: rates and risk factors, *Diabetes Care*, **20**(1): 36–44.

- Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA and Uusitupa MI (2000). Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial, *Medicine & Science in Sports & Exercise*, **32**(9): 1541–1548.
- Lachin JM, Genuth S, Cleary P, Davis MD and Nathan DM (2000). Retinopathy and nephropathy in patients with type I diabetes four years after a trial of intensive therapy, *New England Journal of Medicine*, **342**(6): 381–389.
- Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN and DCCT/EDIC Study Research Group (2008). Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial – revisited, *Diabetes*, **57**(4): 995–1001.
- Laffel L (1999). Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes, *Diabetes/Metabolism Research and Reviews*, **15**(6): 412–426.
- Laffel LMB, Vangsness L, Connell A, Goebel-Fabbri A, Butler D and Anderson BJ (2003). Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes, *Journal of Pediatrics*, **142**(4): 409–416.
- Laffel LMB, Wentzell K, Loughlin C, Tovar A, Moltz K and Brink S (2006). Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: A randomized clinical trial, *Diabetic Medicine*, **23**(3): 278–284.
- Lagarde WH, Barrows FP, Davenport ML, Kang M, Guess HA and Calikoglu AS (2006). Continuous subcutaneous glucose monitoring in children with type 1 diabetes mellitus: a single-blind, randomized, controlled trial, *Pediatric Diabetes*, **7**(3): 159–164.
- Lampeter EF, Klinghammer A, Scherbaum WA, Heinze E, Haastert B, Giani G and Kolb H (1998). The Deutsche Nicotinamide Intervention Study: an attempt to prevent type 1 diabetes. DENIS Group, *Diabetes*, **47**(6): 980–984.
- Landgraf JM, Abetz L and Ware JE (1996). *Child Health Questionnaire (CHQ): A user's manual*, The Health Institute, New England Medical Center, Boston.
- Lang E (2008). *Best practice guidelines for health professionals for the effective transition of young people with diabetes from paediatric to adult care*. Available at: http://www.health.qld.gov.au/cpic/documents/dbtran_bpguide_hp2.pdf.
- Langendam M, Hooft L, Mudde A, de Vries H, Luijf Y, Limpens J and Scholten T (In preparation). Continuous glucose monitoring for diabetes mellitus, *Cochrane Database of Systematic Reviews*.
- Langendam MW, Hooft L, De Vries H, Wentholt IM, Mudde AH, Burt AL and Scholten RJPM (2009). Continuous glucose monitoring systems for type 1 diabetes mellitus, *Cochrane Database of Systematic Reviews*, (4).

- Lanza GA, Pitocco D, Navarese EP, Sestito A, Sgueglia GA, Manto A, Infusino F, Musella T, Ghirlanda G and Crea F (2007). Association between cardiac autonomic dysfunction and inflammation in type 1 diabetic patients: effect of beta-blockade, *European Heart Journal*, **28**(7): 814–820.
- Larsson K, Carlsson A, Cederwall E, Jonsson B, Neiderud J, Lernmark A and Ivarsson SA (2008). Annual screening detects celiac disease in children with type 1 diabetes, *Pediatric Diabetes*, **9**(4 Pt 2): 354–359.
- Lawson ML, Gerstein HC, Tsui E and Zinman B (1999). Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. A systematic review and meta-analysis, *Diabetes Care*, **22**(Suppl 2): B35–39.
- Lee P, Greenfield JR and Campbell LV (2009). Managing young people with Type 1 diabetes in a 'rave' new world: metabolic complications of substance abuse in Type 1 diabetes, *Diabetic Medicine*, **26**(4): 328–333.
- Lemaster JW, Mueller MJ, Reiber GE, Mehr DR, Madsen RW and Conn VS (2008). Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial, *Physical Therapy*, **88**(11): 1385–1398.
- Leslie RD, Kolb H, Schloot NC, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Sarti C, Thivolet C, Hadden D, et al. (2008). Diabetes classification: grey zones, sound and smoke: Action LADA 1, *Diabetes/Metabolism Research and Reviews*, **24**(7): 511–519.
- Levetan CS, Salas JR, Willets IF and Zumoff B (1995). Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes, *American Journal of Medicine*, **99**(1): 22–28.
- Lewis EJ, Hunsicker LG, Bain RP and Rohde RD (1993). The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group, *New England Journal of Medicine*, **329**(20): 1456–1462.
- Li C, Ford ES, Zhao G, Strine TW, Dhingra S, Barker L, Berry JT and Mokdad AH (2009). Association between diagnosed diabetes and serious psychological distress among U.S. adults: the Behavioral Risk Factor Surveillance System, 2007, *International Journal of Public Health*, **54**(Suppl 1): 43–51.
- Li R, Zhang P, Barker LE, Chowdhury FM and Zhang X (2010). Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review, *Diabetes Care*, **33**(8): 1872–1894.
- Libman IM, Pietropaolo M, Arslanian SA, LaPorte RE and Becker DJ (2003). Changing prevalence of overweight children and adolescents at onset of insulin-treated diabetes, *Diabetes Care*, **26**(10): 2871–2875.
- Liesenfeld B, Renner R, Neese M and Hepp KD (2000). Telemedical care reduces hypoglycemias and improves glycemic control in children and adolescents with type 1 diabetes, *Diabetes Technology & Therapeutics*, **2**(4): 561–567.

- Ligtenberg PC, Blans M, Hoekstra JB, van der Tweel I and Erkelens DW (1999). No effect of long-term physical activity on the glycemic control in type 1 diabetes patients: a cross-sectional study, *Netherlands Journal of Medicine*, **55**(2): 59–63.
- Lim A, Cranswick N and South M (2010). Adverse events associated with the use of complementary and alternative medicine in children, *Archives of Disease in Childhood*.
- Lin A, Northam EA, Rankins D, Werther GA and Cameron FJ (2010). Neuropsychological profiles of young people with type 1 diabetes 12 yr after disease onset, *Pediatric Diabetes*, **11**(4): 235–243.
- Logtenberg SJ, Kleefstra N, Groenier KH, Gans RO and Bilo HJ (2009). Use of short-term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: a feasibility study, *Diabetes Technology & Therapeutics*, **11**(5): 293–299.
- Lorenz RA, Santiago JV, Siebert C, Cleary PA and Heyse S (1991). Epidemiology of severe hypoglycemia in the diabetes control and complications trial, *American Journal of Medicine*, **90**(4): 450–459.
- Lormeau B, Sola A, Tabah A, Chiheb S, Dufaitre L, Thurninger O, Bresson R, Lormeau C, Attali JR and Valensi P (2005). Blood glucose changes and adjustments of diet and insulin doses in type 1 diabetic patients during scuba diving (for a change in French regulations), *Diabetes & Metabolism*, **31**(2): 144–151.
- Loveman E, Cave C, Green C, Royle P, Dunn N and Waugh N (2003). The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation, *Health Technology Assessment*, **7**(22): iii, 1–190.
- Ludvigsson J and Hanas R (2003). Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study, *Pediatrics*, **111**(5 Pt 1): 933–938.
- Ludvigsson J, Samuelsson U, Johansson C and Stenhammar L (2001). Treatment with antioxidants at onset of type 1 diabetes in children: A randomized, double-blind placebo-controlled study, *Diabetes/Metabolism Research and Reviews*, **17**(2): 131–136.
- Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, Parving I, Pietraszek L, Frandsen M, Rossing P, et al. (2008). Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study, *PLoS ONE [Electronic Resource]*, **3**(10).
- Lustman PJ, Clouse RE, Griffith LS, Carney RM and Freedland KE (1997). Screening for depression in diabetes using the Beck Depression Inventory, *Psychosomatic Medicine*, **59**(1): 24–31.
- Ly D, Fu AZ and Hebert C (2009). Cost effectiveness analysis of a hypertension management program in patients with type 2 diabetes, *Journal of clinical hypertension (Greenwich, Conn.)*, **11**(3): 116–124.

- Ly TT, Hewitt J, Davey RJ, Lim EM, Davis EA and Jones TW (2011). Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes, *Diabetes Care*.
- Mannucci E, Rotella F, Ricca V, Moretti S, Placidi GF and Rotella CM (2005). Eating disorders in patients with type 1 diabetes: a meta-analysis, *Journal of Endocrinological Investigation*, **28**(5): 417–419.
- Mantovani RM, Mantovani LM and Dias VM (2007). Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors, *Journal of Pediatric Endocrinology*, **20**(6): 669–675.
- Manuel YKB, Van Campenhout C, Vertommen J and De Leeuw I (2003). Effects of Atorvastatin on LDL sub-fractions and peroxidation in type 1 diabetic patients: a randomised double-blind placebo-controlled study, *Diabetes/Metabolism: Research and Reviews*, **19**(6): 478–486.
- Manuel YKB, Vinckx M, Vertommen J, Van Gaal L and De Leeuw I (2004). Impact of Vitamin E supplementation on lipoprotein peroxidation and composition in Type 1 diabetic patients treated with Atorvastatin, *Atherosclerosis*, (2): 369–376.
- Maran A, Lomas J, Macdonald IA and Amiel SA (1995). Lack of preservation of higher brain function during hypoglycaemia in patients with intensively-treated IDDM, *Diabetologia*, **38**(12): 1412–1418.
- Marcovecchio ML and Chiarelli F (2010). Microvascular disease in children and adolescents with type 1 diabetes and obesity, *Pediatric Nephrology*, **Aug 19**.
- Marcovecchio ML, Tossavainen PH and Dunger DB (2010). Prevention and treatment of microvascular disease in childhood type 1 diabetes, *British Medical Bulletin*, **94**(145–64).
- Marsh MN and Crowe PT (1995). Morphology of the mucosal lesion in gluten sensitivity, *Baillière's Clinical Gastroenterology*, **9**(2): 273–293.
- Marshall G, McDougall C, Brady AJB and Fisher M (2004). Should all diabetic patients receive a statin? Results from recent trials, *British Journal of Cardiology*, **11**(6): 455–460.
- Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, Drummond K, Donnelly S, Goodyer P, Gubler MC, et al. (2009). Renal and retinal effects of enalapril and losartan in type 1 diabetes, *New England Journal of Medicine*, **361**(1): 40–51.
- May C, Montori VM and Mair FS (2009). We need minimally disruptive medicine, *British Medical Journal*, **339**: b2803.
- McCabe CJ, Stevenson RC and Dolan AM (1998). Evaluation of a diabetic foot screening and protection programme, *Diabetic Medicine*, **15**(1): 80–84.
- McDonagh JE and Viner RM (2006). Lost in transition? Between paediatric and adult services, *British Medical Journal*, **332**(7539): 435–436.

- McElduff A, Cheung NW, McIntyre HD, Lagström JA, Oats JJ, Ross GP, Simmons D, Walters BN, Wein P and Australasian Diabetes in Pregnancy Society (2005). The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy, *Medical Journal of Australia*, **183**(7): 373–377.
- McElvy SS, Miodovnik M, Rosenn B, Khoury JC, Siddiqi T, Dignan PS and Tsang RC (2000). A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels, *Journal of Maternal-Fetal Medicine*, **9**(1): 14–20.
- McGill M, Molyneaux L, Twigg SM and Yue DK (2008). The metabolic syndrome in type 1 diabetes: does it exist and does it matter?, *Journal of Diabetes & its Complications*, **22**(1): 18–23.
- McIntyre HD (2006). DAFNE (Dose Adjustment for Normal Eating): Structured education in insulin replacement therapy for type 1 diabetes, *Medical Journal of Australia*, **184**(7): 317–318.
- McLachlan K, Jenkins A and O'Neal D (2007). The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy, *Australian and New Zealand Journal of Obstetrics and Gynaecology*, **47**(3): 186–190.
- McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, Fournier PA and Jones TW (2007). Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner, *Journal of Clinical Endocrinology & Metabolism*, **92**(3): 963–968.
- Melendez-Ramirez LY, Richards RJ and Cefalu WT (2010). Complications of type 1 diabetes., *Endocrinology & Metabolism Clinics of North America*, **39**(3): 625–640.
- Meloche RM (2007). Transplantation for the treatment of type 1 diabetes, *World Journal of Gastroenterology*, **13**(47): 6347–6355.
- Meyer L, Bohme P, Delbachian I, Lehert P, Cugnardey N, Drouin P and Guerci B (2002). The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients, *Diabetes Care*, **25**(12): 2153–2158.
- Middleton P, Crowther CA, Simmonds L and Muller P (2010). Different intensities of glycaemic control for pregnant women with pre-existing diabetes, *Cochrane Database of Systematic Reviews*, (9): CD008540.
- Miodovnik M, Mimouni F, St. John Dignan P, Berk MA, Ballard JL and Siddiqi TA (1988). Major malformations in infants of IDDM women: vasculopathy and early first-trimester poor glycemic control, *Diabetes Care*, **11**: 713–718.
- Misso ML, Egberts KJ, Page M, O'Connor D and Shaw J (2010). Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus, *Cochrane Database of Systematic Reviews*, (1): CD005103.
- Mitchell TH, Abraham G, Schiffrin A, Leiter LA and Marliss EB (1988). Hyperglycemia after intense exercise in IDDM subjects during continuous subcutaneous insulin infusion, *Diabetes Care*, **11**(4): 311–317.

- Mohsin F, Craig ME, Cusumano J, Chan AK, Hing S, Lee JW, Silink M, Howard NJ and Donaghue KC (2005). Discordant trends in microvascular complications in adolescents with type 1 diabetes from 1990 to 2002, *Diabetes Care*, **28**(8): 1974–1980.
- Mortensen HB and Hougaard P (1997). Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with IDDM from 18 countries. The Hvidovre Study Group on Childhood Diabetes, *Diabetes Care*, **20**(5): 714–720.
- Moulik PK, Mtonga R and Gill GV (2003). Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology, *Diabetes Care*, **26**(2): 491–494.
- Mullen MJ, Wright D, Donald AE, Thorne S, Thomson H and Deanfield JE (2000). Atorvastatin but not L-arginine improves endothelial function in type I diabetes mellitus: a double-blind study, *Journal of the American College of Cardiology*, **36**(2): 410–416.
- Mullins P, Sharplin P, Yki-Jarvinen H, Riddle MC and Haring HU (2007). Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven Phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus, *Clinical Therapeutics*, **29**(8): 1607–1619.
- Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, Fowler D, Campbell PJ and Temple RC (2008). Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial, *British Medical Journal*, **337**: a1680.
- Murray HJ, Young MJ, Hollis S and Boulton AJ (1996). The association between callus formation, high pressures and neuropathy in diabetic foot ulceration, *Diabetic Medicine*, **13**(11): 979–982.
- Musen G, Jacobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Dahms W, Bayless M, Silvers N, Harth J, et al. (2008). Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial, *Diabetes Care*, **31**(10): 1933–1938.
- Naguib JM, Kulinskaya E, Lomax CL and Garralda ME (2009). Neuro-cognitive performance in children with type 1 diabetes--a meta-analysis, *Journal of Pediatric Psychology*, **34**(3): 271–282.
- Nakhla M, Daneman D, To T, Paradis G and Guttman A (2009). Transition to adult care for youths with diabetes mellitus: findings from a Universal Health Care System, *Pediatrics*, **124**(6): e1134–1141.
- Namba M, Hanafusa T, Kono N and Tarui S (1993). Clinical evaluation of biosynthetic glucagon treatment for recovery from hypoglycemia developed in diabetic patients. The GL-G Hypoglycemia Study Group, *Diabetes Research & Clinical Practice*, **19**(2): 133–138.
- Nanto-Salonen K, Kupila A, Simell S, Siljander H, Salonsaari T, Hekkala A, Korhonen S, Erkkola R, Sipila JJ, Haavisto L, et al. (2008). Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial, *Lancet*, **372**(9651): 1746–1755.

- Nardi L, Zucchini S, D'Alborton F, Salardi S, Maltoni G, Bisacchi N, Elleri D and Cicognani A (2008). Quality of life, psychological adjustment and metabolic control in youths with type 1 diabetes: a study with self- and parent-report questionnaires, *Pediatric Diabetes*, **9**(5): 496–503.
- Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B and DCCT/EDIC Study Research Group (2005). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *New England Journal of Medicine*, **353**(25): 2643–2653.
- Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D and Heine RJ (2008). Translating the A1C assay into estimated average glucose values, *Diabetes Care*, **31**(8): 1473-1478.
- Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH and Genuth S (2003). Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus, *New England Journal of Medicine*, **348**(23): 2294–2303.
- Nathan DM, Zinman B, Cleary PA, Backlund JYC, Genuth S, Miller R and Orchard TJ (2009). Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: The diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005), *Archives of Internal Medicine*, **169**(14): 1307–1316.
- National Health Priority Action Council (2006). *National Service Improvement Framework for Diabetes*, Canberra, Australian Government Department of Health and Ageing.
- National High Blood Pressure Education Program (2004). *The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*, Bethesda (MD): National Heart, Lung, and Blood Institute (US).
- NHMRC (National Health and Medical Research Council) (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines*, NHMRC. Available at: <http://www.nhmrc.gov.au/publications/synopses/cp30syn.htm>.
- NHMRC (National Health and Medical Research Council) (2000). *How to review the evidence: systematic identification and review of the scientific literature*, NHMRC. Available at: www.nhmrc.gov.au/publications/synopses/cp65syn.htm.
- NHMRC (National Health and Medical Research Council) (2007). *NHMRC standards and procedures for externally developed guidelines*, NHMRC. Available at: <http://www.nhmrc.gov.au/publications/synopses/nh56syn.htm>.
- NHMRC (National Health and Medical Research Council) (2009). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*, NHMRC. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf.
- NICE (National Institute for Clinical Excellence) (2009). *Coeliac disease: recognition and assessment of coeliac disease*, National Institute for Health and Clinical Excellence. Available at: www.nice.org.uk/CG86.

- NICE (National Institute for Clinical Excellence) (2010). *Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults*, National Institute for Clinical Excellence. Available at: www.nice.org.uk/CG015NICEguideline.
- Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Boomsma F, Damm P and Mathiesen ER (2009). Severe hypoglycaemia during pregnancy in women with type 1 diabetes: possible role of renin-angiotensin system activity?, *Diabetes Research & Clinical Practice*, **84**(1): 61–67.
- Nielsen S (2002). Eating disorders in females with type 1 diabetes: an update of a meta-analysis, *European Eating Disorders Review*, **10**(4): 241–254.
- Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D and Orchard TJ (2001). Mortality trends in type 1 diabetes: the Allegheny County (Pennsylvania) Registry 1965–1999, *Diabetes Care* **24**: 823–827.
- Nordfeldt S, Johansson C, Carlsson E and Hammersjo JA (2003). Prevention of severe hypoglycaemia in type I diabetes: a randomised controlled population study, *Archives of Disease in Childhood*, **88**(3): 240–245.
- Nordfeldt S, Johansson C, Carlsson E and Hammersjo JA (2005). Persistent effects of a pedagogical device targeted at prevention of severe hypoglycaemia: a randomized, controlled study, *Acta Paediatrica*, **94**(10): 1395–1401.
- Nordfeldt S and Ludvigsson J (2002). Self-study material to prevent severe hypoglycaemia in children and adolescents with type 1 diabetes. A prospective intervention study, *Practical Diabetes International*, **19**(5): 131–136.
- Northam EA, Lin A, Finch S, Werther GA and Cameron FJ (2010). Psychosocial well-being and functional outcomes in youth with type 1 diabetes 12 years after disease onset, *Diabetes Care*, **33**(7): 1430–1437.
- Northam EA, Matthews LK, Anderson PJ, Cameron FJ and Werther GA (2005). Psychiatric morbidity and health outcome in Type 1 diabetes—perspectives from a prospective longitudinal study, *Diabetic Medicine*, **22**(2): 152–157.
- Northam EA, Rankins D, Lin A, Wellard RM, Pell GS, Finch SJ, Werther GA and Cameron FJ (2009). Central nervous system function in youth with type 1 diabetes 12 years after disease onset, *Diabetes Care*, **32**(3): 445–450.
- Noutsou M and Georgopoulos A (1999). Effects of simvastatin on fasting and postprandial triglyceride-rich lipoproteins in patients with type I diabetes mellitus, *Journal of Diabetes & its Complications*, **13**(2): 98–104.
- Nuevo R, Dunn G, Dowrick C, Vazquez-Barquero JL, Casey P, Dalgard OS, Lehtinen V and Ayuso-Mateos JL (2009). Cross-cultural equivalence of the Beck Depression Inventory: a five-country analysis from the ODIN study, *Journal of Affective Disorders*, **114**(1–3): 156–162.
- Nyenwe EA, Razavi LN, Kitabchi AE, Khan AN and Wan JY (2010). Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis, *Diabetes Care*, **33**(8): 1837–1839.

- O'Connell MA, Donath S, O'Neal DN, Colman PG, Ambler GR, Jones TW, Davis EA and Cameron FJ (2009). Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: A randomised controlled trial, *Diabetologia*, **52**(7): 1250–1257.
- O'Connell MA, Gilbertson HR, Donath SM and Cameron FJ (2008). Optimizing postprandial glycemia in pediatric patients with type 1 diabetes using insulin pump therapy: impact of glycemic index and prandial bolus type, *Diabetes Care*, **31**(8): 1491–1495.
- O'Connell PJ, Hawthorne WJ, Holmes-Walker DJ, Nankivell BJ, Gunton JE, Patel AT, Walters SN, Pleass HC, Allen RD and Chapman JR (2006). Clinical islet transplantation in type 1 diabetes mellitus: results of Australia's first trial, *Medical Journal of Australia*, **184**(5): 221–225.
- Oikarinen S, Martiskainen M, Tauriainen S, Huhtala H, Ilonen J, Veijola R, Simell O, Knip M and Hyoty H (2011). Enterovirus RNA in blood is linked to the development of type 1 diabetes, *Diabetes*, **60**(1): 2769.
- Olmos PR, Hodgson MI, Maiz A, Manrique M, De Valdes MD, Foncea R, Acosta AM, Emmerich MV, Velasco S, Muniz OP, et al. (2006). Nicotinamide protected first-phase insulin response (FPIR) and prevented clinical disease in first-degree relatives of type-1 diabetics, *Diabetes Research & Clinical Practice*, **71**(3): 320–333.
- Oipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M and Foster C (2007). Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus, *Pediatric Diabetes*, **8**(6): 377–383.
- Orban T, Sosenko JM, Cuthbertson D, Krischer JP, Skyler JS, Jackson R, Yu L, Palmer JP, Schatz D and Eisenbarth G (2009). Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial-Type 1, *Diabetes Care*, **32**(12): 2269–2274.
- Orchard TJ, Secrest AM, Miller RG and Costacou T (2010). In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study, *Diabetologia*, **53**(11): 2312–2319.
- Overby NC, Flaaten V, Veierod MB, Bergstad I, Margeirsdottir HD, Dahl-Jorgensen K and Andersen LF (2007). Children and adolescents with type 1 diabetes eat a more atherosclerosis-prone diet than healthy control subjects, *Diabetologia*, **50**(2): 307–316.
- Overland J, Molyneaux L, Tewari S, Fatouros R, Melville P, Foote D, Wu T and Yue DK (2009a). Lipohypertrophy: does it matter in daily life? A study using a continuous glucose monitoring system, *Diabetes Obesity and Metabolism*, **11**(5): 460–463.
- Overland J, Sluis M and Reyna R (Eds.) 2009b. *Straight to the point*, Juvenile Diabetes Research Foundation.
- Pacaud D, Yale JF, Stephure D, Trussell R and Davies HD (2005). Problems in transition from pediatric care to adult care for individuals with diabetes, *Canadian Journal of Diabetes Care*, **29**: 13–18.

- Palmer AJ, Roze S, Valentine WJ, Smith I and Wittrup-Jensen KU (2004). Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials, *Current Medical Research & Opinion*, **20**(11): 1729–1746.
- Palmer AJ, Valentine WJ, Ray JA, Foos V, Lurati F, Smith I, Lammert M and Roze S (2007). An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK, *Current Medical Research & Opinion*, **23**(4): 895–901.
- Pambianco G, Costacou T and Orchard TJ (2007). The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience, *Diabetes Care*, **30**(5): 1248–1254.
- Pan Y, Guo LL and Jin HM (2008). Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials, *American Journal of Clinical Nutrition*, **88**(3): 660–666.
- Pankowska E, Blazik M, Dziechciarz P, Szybowska A and Szajewska H (2009). Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials, *Pediatric Diabetes*, **10**(1): 52–58.
- Parving HH, Hommel E, Damkjaer Nielsen M and Giese J (1989). Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy, *British Medical Journal*, **299**(6698): 533–536.
- Patterson CC, Dahlquist GG, Gyurus E, Green A and Soltesz G (2009). Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study, *Lancet*, **373**(9680): 2027–2033.
- Pearson DWM, Kernaghan D, Lee R, Penney GC and Scottish Diabetes in Pregnancy Study G (2007). The relationship between pre-pregnancy care and early pregnancy loss, major congenital anomaly or perinatal death in type I diabetes mellitus, *BJOG: An International Journal of Obstetrics & Gynaecology*, **114**(1): 104–107.
- Pearson T (2008). Glucagon as a treatment of severe hypoglycemia: safe and efficacious but underutilized, *Diabetes Educator*, **34**(1): 128–134.
- Pedersen-Bjergaard U, Dhamrait SS, Sethi AA, Frandsen E, Nordestgaard BG and Montgomery HE (2008). Genetic variation and activity of the renin-angiotensin system and severe hypoglycemia in type 1 diabetes, *American Journal of Medicine*, **121**(3): 246 e241–248.
- Pena AS, Wiltshire E, Gent R, Hirte C and Couper J (2004). Folic acid improves endothelial function in children and adolescents with type 1 diabetes, *Journal of Pediatrics*, **144**(4): 500–504.
- Pendergast DR, Meksawan K, Limprasertkul A and Fisher NM (2010). Influence of exercise on nutritional requirements, *European Journal of Applied Physiology*, **Nov 16**.

- Perez A, Wagner AM, Carreras G, Gimenez G, Sanchez-Quesada JL, Rigla M, Gomez-Gerique JA, Pou JM and de Leiva A (2000). Prevalence and phenotypic distribution of dyslipidemia in type 1 diabetes mellitus: effect of glycemic control, *Archives of Internal Medicine*, **160**(18): 2756–2762.
- Perros P, McCrimmon RJ, Shaw G and Frier BM (1995). Frequency of thyroid dysfunction in diabetic patients: value of annual screening, *Diabetic Medicine*, **12**(7): 622–627.
- Perry L, Steinbeck KS, Dunbabin JS and Lowe JM (2010). Lost in transition? Access to and uptake of adult health services and outcomes for young people with type 1 diabetes in regional New South Wales, *Medical Journal of Australia*, **193**(8): 444–449.
- Petrak F, Hardt J, Wittchen HU, Kulzer B, Hirsch A, Hentzelt F, Borck K, Jacobi F, Egle UT and Hoffmann SO (2003). Prevalence of psychiatric disorders in an onset cohort of adults with type 1 diabetes, *Diabetes/Metabolism Research Reviews*, **19**(3): 216–222.
- Peyrot M and Rubin RR (2009). Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system, *Diabetes Technology & Therapeutics*, **11**(1): 57–62.
- Pham A, Donaghue KC, Chan AK and Craig ME (2010). Younger age at diagnosis of type 1 diabetes increases risk of celiac disease, *Pediatric Diabetes*, **11**(Suppl 14): 22.
- Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA and Robertson LI (2007). Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy, *Diabetic Medicine*, **24**(6): 635–642.
- Pihoker C, Forsander G, Wolfsdorf J and Klingensmith GJ (2009). The delivery of ambulatory diabetes care to children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 58–70.
- Pilkington K, Stenhouse E, Kirkwood G and Richardson J (2007). Diabetes and complementary therapies: mapping the evidence, *Practical Diabetes International*, **24**(7): 371–376.
- Pitocco D, Crino A, Di Stasio E, Manfrini S, Guglielmi C, Spera S, Anguissola GB, Visalli N, Suraci C, Matteoli MC, et al. (2006). The effects of calcitriol and nicotinamide on residual pancreatic beta-cell function in patients with recent-onset Type 1 diabetes (IMDIAB XI), *Diabetic Medicine*, **23**(8): 920–923.
- Plougmann S, Hejlesen O, Turner B, Kerr D and Cavan D (2002). Modelling the effect of alcohol in Type 1 diabetes, *Studies in Health Technology & Informatics*, **90**: 66–71.
- Pollock NW (2009). Correspondance concerning the article "Safety of recreational scuba diving in type 1 diabetic patients: The Deep Monitoring programme", *Diabetes & Metabolism*, **35**(4): 336–337.
- Poole H, Bramwell R and Murphy P (2009). The utility of the Beck Depression Inventory Fast Screen (BDI-FS) in a pain clinic population, *European Journal of Pain*, **13**(8): 865–869.

- Pop-Busui R, Low PA, Waberski BH, Martin CL, Albers JW, Feldman EL, Sommer C, Cleary PA, Lachin JM, Herman WH, et al. (2009). Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC), *Circulation*, **119**(22): 2886–2893.
- Poulain C, Johanet C, Delcroix C, Levy-Marchal C and Tubiana-Rufi N (2007). Prevalence and clinical features of celiac disease in 950 children with type 1 diabetes in France, *Diabetes & Metabolism*, **33**(6): 453–458.
- Pozzilli P, Browne PD and Kolb H (1996). Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. The Nicotinamide Trialists, *Diabetes Care*, **19**(12): 1357–1363.
- Pratoomsot C, Smith HT, Kalsekar A, Boye KS, Arellano J and Valentine WJ (2009). An estimation of the long-term clinical and economic benefits of insulin lispro in Type 1 diabetes in the UK, *Diabetic Medicine*, **26**(8): 803–814.
- Premaratne E, Maclsaac RJ, Finch S, Panagiotopoulos S, Ekinci E and Jerums G (2008). Serial measurements of cystatin C are more accurate than creatinine-based methods in detecting declining renal function in type 1 diabetes, *Diabetes Care*, **35**(5): 971–973.
- Purnell JQ, Hokanson JE, Marcovina SM, Steffes MW, Cleary PA and Brunzell JD (1998). Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial, *Journal of the American Medical Association*, **280**(2): 140–146.
- Rabasa-Lhoret R, Bourque J, Ducros F and Chiasson JL (2001). Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro), *Diabetes Care*, **24**(4): 625–630.
- Racah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H, Jeandidier N and Nicolino M (2009). Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study, *Diabetes Care*, **32**(12): 2245–2250.
- Radberg T, Gustafson A, Skryten A and Karlsson K (1982). Oral contraception in diabetic women. A cross-over study on serum and high density lipoprotein (HDL) lipids and diabetes control during progestogen and combined estrogen/progestogen contraception, *Hormone & Metabolic Research*, **14**: 61–65.
- Ramchandani N, Cantey-Kiser JM, Alter CA, Brink SJ, Yeager SD, Tamborlane WV and Chipkin SR (2000). Self-reported factors that affect glycemic control in college students with type 1 diabetes, *Diabetes Educ*, **26**(4): 656–666.
- Rasli MHM and Zacharin MR (2008). Foot problems and effectiveness of foot care education in children and adolescents with diabetes mellitus, *Pediatric Diabetes*, **9**(6): 602–608.
- Ray JG, O'Brien TE and Chan WS (2001). Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis, *Quarterly Journal of Medicine*, **94**(8): 435–444.

- Reality Check (2005). *A starter kit for recently diagnosed adult diabetes*, Reality Check. Available at: <http://www.realitycheck.org.au/starterkit>.
- Reichard P (1996). To be a teacher, a tutor and a friend: the physician's role according to the Stockholm Diabetes Intervention Study (SDIS), *Patient Educ Couns*, **29**(3): 231–235.
- Reichard P, Alm C, Andersson E, Warn I and Rosenqvist U (1999). Intensified insulin treatment is cost-effective, *Lakartidningen*, **96**(3): 172–174.
- Reichard P, Pihl M, Rosenqvist U and Sule J (1996). Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up, *Diabetologia*, **39**(12): 1483–1488.
- Reviriego J, Gomis R, Maranes JP, Ricart W, Hudson P and Sacristan JA (2008). Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia, *International Journal of Clinical Practice*, **62**(7): 1026–1032.
- Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M and Rewers M (2002). Predictors of acute complications in children with type 1 diabetes, *Journal of the American Medical Association*, **19**(287): 2511–2518.
- Rewers M, Pihoker C, Donaghue K, Hanas R, Swift P and Klingensmith GJ (2009). Assessment and monitoring of glycemic control in children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 71–81.
- Richardson SJ, Willcox A, Bone AJ, Foulis AK and Morgan NG (2009). The prevalence of enteroviral capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes, *Diabetologia*, **52**(6): 1143–1151.
- Riddell M and Perkins BA (2009). Exercise and glucose metabolism in persons with diabetes mellitus: perspectives on the role for continuous glucose monitoring, *Journal of Diabetes Science & Technology*, **3**(4): 914–923.
- Riddell MC and Iscoe KE (2006). Physical activity, sport, and pediatric diabetes, *Pediatr Diabetes*, **7**(1): 60–70.
- Rivkees SA and Mattison DR (2009). Ending propylthiouracil-induced liver failure in children, *New England Journal of Medicine*, **360**(15): 1574–1575.
- Robertson H, Pearson DW and Gold AE (2009a). Severe hypoglycaemia during pregnancy in women with Type 1 diabetes is common and planning pregnancy does not decrease the risk, *Diabetic Medicine*, **26**(8): 824–826.
- Robertson K, Adolfsson P, Scheiner G, Hanas R and Riddell MC (2009b). ISPAD clinical practice consensus guidelines 2009 compendium. Exercise in children and adolescents with diabetes, *Pediatr Diabetes*, **10**(Suppl 12): 154–168.
- Robertson LN, Waugh N and Robertson A (2009c). Protein restriction for diabetic renal disease (Review), *Cochrane Database of Systematic Reviews*, (1): CD002181.

- Rogovskaya S, Rivera R, Grimes DA, Chen PL, Pierre-Louis B, Prilepskaya V and Kulakov V (2005). Effect of a levonorgestrel intrauterine system on women with type 1 diabetes: a randomized trial, *Obstetrics & Gynecology*, **4**: 811–815.
- Rolim LC, Sa JR, Chacra AR and Dib SA (2008). Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis, *Arquivos Brasileiros de Cardiologia*, **90**(4): e24–31.
- Rosenfalck AM, Almdal T, Viggers L, Madsbad S and Hilsted J (2006). A low-fat diet improves peripheral insulin sensitivity in patients with Type 1 diabetes, *Diabetic Medicine*, **23**(4): 384–392.
- Roy MS, Klein R, O'Colmain BJ, Klein BE, Moss SE and Kempen JH (2004). The prevalence of diabetic retinopathy among adult type 1 diabetic persons in the United States, *Archives of Ophthalmology*, **122**(4): 546–551.
- Royal College of Physicians of Edinburgh Transition Steering Group (2008). *Think Transition: developing the essential link between paediatric and adult care*, Edinburgh, Scotland, Royal College of Physicians. Available at: <http://www.rcpe.ac.uk/clinical-standards/documents/transition.pdf>.
- Roze S, Valentine WJ, Zakrzewska KE and Palmer AJ (2005). Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK, *Diabetic Medicine*, **22**(9): 1239–1245.
- Rustemeijer C, Schouten JA, Janssens EN, Spooren PF and van Doormaal JJ (1997). Pravastatin in diabetes-associated hypercholesterolemia, *Acta Diabetologica*, **34**(4): 294–300.
- Sacks DA, Feig DS, Liu IL and Wolde-Tsadik G (2006). Managing type I diabetes in pregnancy: how near normal is necessary?, *Journal of Perinatology*, **26**(8): 458–462.
- Salardi S, Volta U, Zucchini S, Fiorini E, Maltoni G, Vaira B and Cicognani A (2008). Prevalence of celiac disease in children with type 1 diabetes mellitus increased in the mid-1990s: an 18-year longitudinal study based on anti-endomysial antibodies, *Journal of Pediatric Gastroenterology & Nutrition*, **46**(5): 612–614.
- Salmeron J, Jenkins DJ, Ascerio A, Stampfer MJ and Rimm EB (1997). Dietary fiber, glycemic load and risk of NIDDM in men, *Diabetes Care*, **20**: 545–550.
- Salti I, Benard E, Detournay B, Bianchi-Biscay M, Le Brigand C and Voinet C (2004). A populationbased study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study, *Diabetes Care*, **27**(10): 2306–2311.
- Samann A, Muhlhauser I, Bender R, Kloos C and Muller UA (2005). Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study, *Diabetologia*, **48**(10): 1965–1970.
- Sandoval DA, Guy DL, Richardson MA, Ertl AC and Davis SN (2004). Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes, *Diabetes Care*, **53**(7): 1798–1806.

- Särnblad S, Ekelund U and Aman J (2005). Physical activity and energy intake in adolescent girls with Type 1 diabetes, *Diabetic Medicine*, **22**(7): 893–899.
- Särnblad S, Kroon M and Aman J (2003). Metformin as additional therapy in adolescents with poorly controlled type 1 diabetes: randomised placebo-controlled trial with aspects on insulin sensitivity, *European Journal of Endocrinology*, **149**(4): 323–329.
- Scavone G, Manto A, Pitocco D, Gagliardi L, Caputo S, Mancini L, Zaccardi F and Ghirlanda G (2010). Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in Type 1 diabetic subjects: A pilot study, *Diabetic Medicine*, **27**(4): 477–479.
- Schachinger H, Hegar K, Hermanns N, Straumann M, Keller U and Fehm-Wolfsdorf G (2005). Randomized controlled clinical trial of blood glucose awareness training (BGAT III) in Switzerland and Germany, *Journal of Behavioral Medicine*, **28**(6): 587–594.
- Schutt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R, Mayer I, Rosenbauer J, Wagner C, Zimmermann A, et al. (2006). Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24 500 patients from 191 centers in Germany and Austria, *Experimental & Clinical Endocrinology & Diabetes*, **114**(7): 384–388.
- Schwartz L (2009). Therapeutic options in coronary artery disease: focusing on the guidelines, *Canadian Journal of Cardiology*, **25**(1): 19–24.
- Secrest AM, Becker DJ, Kelsey SF, LaPorte RE and Orchard TJ (2010a). All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry, *Diabetes Care*, **33**(12): 2573–2579.
- Secrest AM, Becker DJ, Kelsey SF, Laporte RE and Orchard TJ (2010b). Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes, *Diabetes*, **59**(12): 3216–3222.
- Serraclara A, Hawkins F, Perez C, Dominguez E, Campillo JE and Torres MD (1998). Hypoglycemic action of an oral fig-leaf decoction in type-I diabetic patients, *Diabetes Research & Clinical Practice*, **39**(1): 19–22.
- Severinski S, Banac S, Severinski NS, Ahel V and Cvijovic K (2009). Epidemiology and clinical characteristics of thyroid dysfunction in children and adolescents with type 1 diabetes, *Collegium Antropologicum*, **33**(1): 273–279.
- Sharma RD, Raghuram TC and Sudhakar N (1990). Effect of fenugreek seeds on blood glucose and serum lipids in Type 1 diabetes, *European Journal of Clinical Nutrition*, **44**: 301–306.
- Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, Schwenk WF and Miles JM (2008). Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis?, *Diabetes Care*, **31**(4): 643–647.

- Shephard MD and Gill JP (2003). Results of an innovative education, training and quality assurance program for point-of-care HbA1c testing using the Bayer DCA 2000 in Australian Aboriginal Community Controlled Health Services, *Clin Biochem Rev*, **24**(4): 123-130.
- Sibal L, Law HN, Gebbie J, Dashora UK, Agarwal SC and P. H (2006). Predicting the development of macrovascular disease in people with type 1 diabetes: A 9-year follow-up study, *Annals of the New York Academy of Sciences*, **1084**: 191–207.
- Siminerio LM, Charron-Prochownik D, Banion C and Schreiner B (1999). Comparing outpatient and inpatient diabetes education for newly diagnosed pediatric patients, *Diabetes Educator*, **25**(6): 895–906.
- Simmons JH, Klingensmith GJ, McFann K, Rewers M, Taylor J, Emery LM, Taki I, Vanyi S, Liu E and Hoffenberg EJ (2007). Impact of celiac autoimmunity on children with type 1 diabetes, *Journal of Pediatrics*, **150**(5): 461–466.
- Simmons JH, Zeitler PS, Fenton LZ, Abzug MJ, Fiallo-Scharer RV and Klingensmith GJ (2005). Rhinocerebral mucormycosis complicated by internal carotid artery thrombosis in a pediatric patient with type 1 diabetes mellitus: a case report and review of the literature, *Pediatric Diabetes*, **6**(4): 234–238.
- Simpson TC, Needleman I, Wild SH, Moles DR and Mills EJ (2010). Treatment of periodontal disease for glycaemic control in people with diabetes, *Cochrane Database of Systematic Reviews*, (5): CD004714.
- Singh SR, Ahmad F, Lal A, Yu C, Bai Z and Bennett H (2009). Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis, *Canadian Medical Association Journal*, **180**(4): 385–397.
- Skinner TC (2002). Recurrent diabetic ketoacidosis: causes, prevention and management, *Hormone Research*, **57**(Suppl 1): 78–80.
- Skouby SO, Molsted-Pedersen L, Kuhl C and Bennet P (1986). Oral contraceptives in diabetic women: metabolic effects of four compounds with different estrogen/progestogen profiles, *Fertility & Sterility*, **46**(5): 858–864.
- Skyler JS (2008). Update on worldwide efforts to prevent type 1 diabetes, *Annals of the New York Academy of Sciences*, **1150**: 190–196.
- Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, Cuthbertson D, Rafkin-Mervis LE, Chase HP and Leschek E (2005). Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial--Type 1, *Diabetes Care*, **28**(5): 1068–1076.
- Smart C, Aslander-van Vliet E and Waldron S (2009). Nutritional management in children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 100–117.
- Smith CB, Choudhary P, Pernet A, Hopkins D and Amiel SA (2009). Hypoglycemia unawareness is associated with reduced adherence to therapeutic decisions in patients with type 1 diabetes: evidence from a clinical audit, *Diabetes Care*, **32**(7): 1196–1198.

- Snell-Bergeon JK, Chartier-Logan C, Maahs DM, Ogden LG, Hokanson JE, Kinney GL, Eckel RH, Ehrlich J and Rewers M (2009). Adults with type 1 diabetes eat a high-fat atherogenic diet that is associated with coronary artery calcium, *Diabetologia* **52**(5): 801–809.
- Snoek FJ, Van Der Ven NCW, Twisk JWR, Hogenelst MHE, Tromp-Wever AME, Van Der Ploeg HM and Heine RJ (2008). Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: Long-term effects on HbA1c moderated by depression. A randomized controlled trial, *Diabetic Medicine*, **25**(11): 1337–1342.
- Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH and EURODIAB Prospective Complications Study Group (2008). Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS), *Diabetes Care*, **31**(7): 1360–1366.
- Somers EC, Thomas SL, Smeeth L and Hall AJ (2009). Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder?, *American Journal of Epidemiology*, **169**(6): 749–755.
- Srinivasan S, Craig ME, Beeney L, Hayes R, Harkin N, Ambler GR, Donaghue KC and Cowell CT (2004). An ambulatory stabilisation program for children with newly diagnosed type 1 diabetes, *Medical Journal of Australia*, **180**(6): 277–280.
- St Charles M, Lynch P, Graham C and Minshall ME (2009). A cost-effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: A third-party US payer perspective, *Value in Health*, **12**(5): 674–686.
- Stene LC, Oikarinen S, Hyoty H, Barriga KJ, Norris JM, Klingensmith G, Hutton JC, Erlich HA, Eisenbarth GS and Rewers M (2010). Enterovirus infection and progression from islet autoimmunity to type 1 diabetes: the Diabetes and Autoimmunity Study in the Young (DAISY), *Diabetes*, **59**(12): 3174–3180.
- Stephenson JM, Kempler P, Perin PC and Fuller JH (1996). Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study, *Diabetologia*, **39**(11): 1372–1376.
- Stettler C, Allemann S, Juni P, Cull CA, Holman RR, Egger M, Krahenbuhl S and Diem P (2006). Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials, *American Heart Journal*, **152**(1): 27–38.
- Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR and the UKPDS Group (2001). The UKPDS risk engine: a model for the risk of coronary heart disease in type 2 diabetes UKPDS 56, *Clinical Science*, **101**: 671–679.
- Stone ML, Craig ME, Chan AK, Lee JW, Verge CF and Donaghue KC (2006). Natural history and risk factors for microalbuminuria in adolescents with type 1 diabetes: a longitudinal study, *Diabetes Care*, **29**(9): 2072–2077.
- Strudwick SK, Carne C, Gardiner J, Foster JK, Davis EA and Jones TW (2005). Cognitive functioning in children with early onset type 1 diabetes and severe hypoglycemia, *Journal of Pediatrics*, **147**(5): 680–685.

- Strychar I, Cohn JS, Renier G, Rivard M, Aris-Jilwan N, Beauregard H, Meltzer S, Belanger A, Dumas R, Ishac A, et al. (2009). Effects of a diet higher in carbohydrate/lower in fat versus lower in carbohydrate/higher in monounsaturated fat on postmeal triglyceride concentrations and other cardiovascular risk factors in type 1 diabetes, *Diabetes Care*, **32**(9): 1597–1599.
- Strychar I, Ishac A, Rivard M, Lussier-Cacan S, Beauregard H, Aris-Jilwan N, Radwan F and Yale JF (2003). Impact of a high-monounsaturated-fat diet on lipid profile in subjects with type 1 diabetes, *Journal of the American Dietetic Association*, **103**(4): 467–474.
- Suys BE, Katier N, Rooman RP, Matthys D, Op De Beeck L, Du Caju MV and De Wolf D (2004). Female children and adolescents with type 1 diabetes have more pronounced early echocardiographic signs of diabetic cardiomyopathy, *Diabetes Care*, **27**(8): 1947–1953.
- Svoren BM, Butler D, Levine BS, Anderson BJ and Laffel LMB (2003). Reducing acute adverse outcomes in youths with type 1 diabetes: A randomized, controlled trial, *Pediatrics*, **112**(4): 914–922.
- Swift PG (2009). Diabetes education in children and adolescents, *Pediatric Diabetes*, **10**(Suppl 12): 51–57.
- Swift PGF, Hearnshaw JR, Botha JL, Wright G, Raymond NT and Jamieson KF (1993). A decade of diabetes: Keeping children out of hospital, *British Medical Journal*, **307**(6896): 96–98.
- Swislocki AL and Siegel D (2001). Renal effects of angiotensin-converting enzyme inhibitors that result in cost savings and improved patient outcomes, *American Journal of Managed Care*, **7**(3): 283–295.
- Tanenbergs R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP, Tobian J, Gross T and Mastrototaro J (2004). Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial, *Mayo Clinic Proceedings*, **79**(12): 1521–1526.
- Tang T, Lord JM, Norman RJ, Yasmin E and Balen AH (2010). Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility, *Cochrane Database of Systematic Reviews*, (1): CD003053.
- Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, Janz KF, Kollman C, Xing D, Ruedy KJ, et al. (2006). The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes, *Diabetes Care*, **29**(1): 20–25.
- Taplin CE, Cobry E, Messer L, McFann K, Chase HP and Fiallo-Scharer R (2010). Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes, *Journal of Pediatrics*, **157**(5): 784–778.
- Taplin CE, Craig ME, Lloyd M, Taylor C, Crock P, Silink M and Howard NJ (2005). The rising incidence of childhood type 1 diabetes in New South Wales, 1990–2002, *Med J Aust*, **183**(5): 243–246.

- Tapp RJ, Shaw JE, de Courten MP, Dunstan DW, Welborn TA and Zimmet PZ (2003). Foot complications in type 2 diabetes: an Australian population-based study, *Diabetic Medicine*, **20**(2): 105–113.
- Temple RC, Aldridge V, Stanley K and Murphy HR (2006). Glycaemic control throughout pregnancy and risk of pre-eclampsia in women with type I diabetes, *BJOG: An International Journal of Obstetrics & Gynaecology*, **113**(11): 1329–1332.
- Terent A, Hagfall O and Cederholm U (1985). The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a representative population, *Acta Medica Scandinavica*, **217**(1): 47–53.
- Thomas D and Elliott EJ (2009). Low glycaemic index, or low glycaemic load, diets for diabetes mellitus, *Cochrane Database of Systematic Reviews*, (1): CD006296.
- Thomas JB, Petrovsky N and Ambler GR (2004). Addison's disease presenting in four adolescents with type 1 diabetes, *Pediatric Diabetes*, **5**(4): 207–211.
- Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ and Shaw JA (2007). A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone, *Diabetic Medicine*, **24**(7): 778–783.
- Toni S, Reali MF, Barni F, Lenzi L and F. F (2006). Managing insulin therapy during exercise in type 1 diabetes mellitus, *Acta BioMedica*, **77**(Suppl 1): 34–40.
- Tran K, Banerjee S, Li H, Cimon K, Daneman D, Simpson SH and Campbell K (2007). *Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of costeffectiveness*, Ottawa, Canadian Agency for Drugs and Technologies in Health (CADTH).
- Tripathi A, Rankin J, Aarvold J, Chandler C and Bell R (2010). Preconception counseling in women with diabetes: A population-based study in the north of England, *Diabetes Care*, **33**(3): 586–588.
- Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzimer SA, Buckingham BA, Kollman C, et al. (2005). Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus, *Journal of Pediatrics*, **147**(4): 528–534.
- Tu E, Bagnall RD, Duflou J, Lynch M, Twigg SM and Semsarian C (2010). Post-mortem pathologic and genetic studies in "dead in bed syndrome" cases in type 1 diabetes mellitus, *Human pathology*, **41**(3): 392–400.
- Tunis SL, Minshall ME, Conner C, McCormick JI, Kapor J, Yale JF and Groleau D (2009). Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis, *Current Medical Research & Opinion*, **25**(5): 1273–1284.
- Tuominen JA, Karonen SL, Melamies L, Bolli G and Koivisto VA (1995). Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue, *Diabetologia*, **38**(1): 106–111.

- Turan S, Omar A and Bereket A (2008). Comparison of capillary blood ketone measurement by electrochemical method and urinary ketone in treatment of diabetic ketosis and ketoacidosis in children, *Acta Diabetologica*, **45**(2): 83–85.
- Type 1 Diabetes TrialNet (2010). *Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus*, Available at: <http://www.diabetestrialnet.org/studies/oral-insulin.htm>.
- UKPDS Group (United Kingdom Prospective Diabetes Study Group) (1998a). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), *Lancet*, **352**(9131): 854–865.
- UKPDS Group (United Kingdom Prospective Diabetes Study Group) (1998b). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), *Lancet* **352**(9131): 837–853.
- Umpierrez GE and Kitabchi AE (2003). Diabetic ketoacidosis: risk factors and management strategies, *Treatments in Endocrinology*, **2**(2): 95–108.
- Umpierrez GE, Latif KA, Murphy MB, Lambeth HC and Stentz FB (2003). Thyroid Dysfunction in Patients With Type 1 Diabetes: A longitudinal study, *Diabetes Care*, **26**: 1181–1185.
- van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G and Dekker JM (2009). Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study, *Diabetes Care*, **32**(11): 2094–2098.
- Vanelli M, Chiari G and Capuano C (2003). Cost effectiveness of the direct measurement of 3-beta-hydroxybutyrate in the management of diabetic ketoacidosis in children, *Diabetes Care*, **26**(3): 959.
- Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM and Petrie JR (2010). The use of metformin in type 1 diabetes: a systematic review of efficacy, *Diabetologia*.
- Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P and Mathiesen ER (2010). Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes, *Diabetic Medicine*, **27**(4): 431–435.
- Victorian CSII Working Party (2009). *Guidelines for continuous subcutaneous insulin infusion (CSII) pump therapy*, Victorian CSII Group. Available at: <http://www.diabetescrc.unimelb.edu.au/professionals/documents/CSIIguidelinesJuly2009-FINAL.pdf>.
- Viklund G, Ortqvist E and Wikblad K (2007). Assessment of an empowerment education programme. A randomized study in teenagers with diabetes, *Diabetic Medicine*, **24**(5): 550–556.
- Viner R (1999). Transition from paediatric to adult care. Bridging the gaps or passing the buck?, *Archives of Disease in Childhood*, **81**: 271–275.

- Viner R (2001). Barriers and good practice in transition from paediatric to adult care, *Journal of the Royal Society of Medicine*, **94**(Suppl 40): 2–4.
- Vinik AI, Maser RE, Mitchell BD and Freeman R (2003). Diabetic autonomic neuropathy, *Diabetes Care*, **26**(5): 1553–1579.
- Visalli N, Cavallo MG, Signore A, Baroni MG, Buzzetti R, Fioriti E, Mesturino C, Fiori R, Lucentini L, Matteoli MC, et al. (1999). A multi-centre randomized trial of two different doses of nicotinamide in patients with recent-onset type 1 diabetes (the IMDIAB VI), *Diabetes/Metabolism Research Reviews*, **15**(3): 181–185.
- Visser J, Snel M and Van Vliet HA (2006). Hormonal versus non-hormonal contraceptives in women with diabetes mellitus type 1 and 2, *Cochrane Database of Systematic Reviews*, (4): CD003990.
- Volzke H, Krohn U, Wallaschofski H, Ludemann J, John U and Kerner W (2007). The spectrum of thyroid disorders in adult type 1 diabetes mellitus, *Diabetes/Metabolism Research Reviews*, **23**(3): 227–233.
- Wake M, Hesketh K and Cameron F (2000). The Child Health Questionnaire in children with diabetes: cross-sectional survey of parent and adolescent-reported functional health status, *Diabetic Medicine*, **17**(10): 700–707.
- Wang B, Carter RE, Jaffa MA, Nakerakanti S, Lackland D, Lopes-Virella M, Trojanowska M, Luttrell LM, Jaffa AA and DCCT/EDIC Study Group (2010). Genetic variant in the promoter of connective tissue growth factor gene confers susceptibility to nephropathy in type 1 diabetes, *Journal of Medical Genetics*, **47**(6): 391–397.
- Wang PH, Lau J and Chalmers TC (1993a). Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes, *Lancet*, **341**(8856): 1306–1309.
- Wang PH, Lau J and Chalmers TC (1993b). Meta-analysis of the effects of intensive glycemic control on late complications of type I diabetes mellitus, *Online Journal of Current Clinical Trials*, **May 21**(60).
- Warncke K, Frohlich-Reiterer EE, Thon A, Hofer SE, Wiemann D and Holl RW (2010). Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database, *Diabetes Care*, **33**(9): 2010–2012.
- Wei CC, Hsu YH, Li HH, Wang YC, Hsieh MY, Chen WY, Hsing CH and Chang MS (2006). IL-20: biological functions and clinical implications, *J Biomed Sci*, **13**(5): 601–612.
- Weintrob N, Schechter A, Benzaquen H, Shalitin S, Lilos P and Galatzer A (2004). Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion, *Archives of Pediatrics & Adolescent Medicine*, **158**: 677–684.
- Weinzimer SA, Ternand C, Howard C, Chang CT, Becker DJ and Laffel LM (2008). A randomized trial comparing continuous subcutaneous insulin infusion of insulin aspart versus insulin lispro in children and adolescents with type 1 diabetes, *Diabetes Care*, **31**(2): 210–215.

- Wentholt IM, Hoekstra JB and Devries JH (2007). Continuous glucose monitors: the long-awaited watch dogs?, *Diabetes Technology & Therapeutics*, **9**(5): 399–409.
- Wheatley CM, Baldi JC, Cassuto NA, Foxx-Lupo WT and Snyder EM (2010). Glycemic control influences lung membrane diffusion and oxygen saturation in exercise-trained subjects with type 1 diabetes: Alveolar-capillary membrane conductance in type 1 diabetes, *European Journal of Applied Physiology*, **October**.
- Whincup G and Milner RD (1987). Prediction and management of nocturnal hypoglycaemia in diabetes, *Archives of Disease in Childhood*, **62**(4): 333–337.
- White NH, Sun W, Cleary PA, Tamborlane WV, Danis RP, Hainsworth DP and Davis MD (2010). Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: Comparison of adults and adolescents, *Diabetes*, **59**(5): 1244–1253.
- WHO (World Health Organization) (2004). *Reproductive Health and Research. Medical Eligibility criteria for contraceptive use*, Geneva, World Health Organization.
- Wiethop BV and Cryer PE (1993). Alanine and terbutaline in treatment of hypoglycemia in IDDM, *Diabetes Care*, **16**(8): 1131–1136.
- Wilkin TJ (2001). The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes, *Diabetologia*, **44**(7): 914–922.
- Wilson DM, Buckingham BA, Kunselman EL, Sullivan MM, Paguntalan HU and Gitelman SE (2005). A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes, *Diabetes Care*, **28**: 15–19.
- Wilson PWF, Castelli WP and Kannel WB (1987). Coronary risk prediction in adults (the Framingham Heart Study), *American Journal of Cardiology*, **59**: 91G–94G.
- Wiltshire EJ, Mohsin F, Chan A and Donaghue KC (2008). Methylenetetrahydrofolate reductase and methionine synthase reductase gene polymorphisms and protection from microvascular complications in adolescents with type 1 diabetes, *Pediatric Diabetes*, **9**(4, Pt 2): 348–353.
- Winkley K, Landau S, Eisler I and Ismail K (2006). Psychological interventions to improve glycaemic control in patients with type 1 diabetes: Systematic review and meta-analysis of randomised controlled trials, *British Medical Journal*, **333**(7558): 65–68.
- Wise JE, Kolb EL and Sauder SE (1992). Effect of glycemic control on growth velocity in children with IDDM, *Diabetes Care*, **15**(7): 826–830.
- Wolever TM, Jenkins DJ, Jenkins AL and Josse RG (1991). The glycemic index: methodology and clinical implications, *American Journal of Clinical Nutrition*, **54**: 846–854.
- Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee W, Rosenbloom A, Sperling M and Hanas R (2009). Diabetic ketoacidosis in children and adolescents with diabetes, *Pediatric Diabetes*, **10**(Suppl 12): 118–133.

- Writing Team for the DCCT/EDIC Research Group (2002). Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus, *Journal of the American Medical Association*, **287**(19): 2563–2569.
- Yamaguchi Y, Chikuba N, Ueda Y, Yamamoto H, Yamasaki H, Nakanishi T, Akazawa S and Nagataki S (1991). Islet cell antibodies in patients with autoimmune thyroid disease, *Diabetes*, **40**(3): 319–322.
- Yates K, Hasnat Milton A, Dear K and Ambler G (2006). Continuous glucose monitoring-guided insulin adjustment in children and adolescents on near-physiological insulin regimens: a randomized controlled trial, *Diabetes Care*, **29**(7): 1512–1517.
- Yeh GY, Eisenberg DM, Kaptchuk TJ and Phillips RS (2003). Systematic review of herbs and dietary supplements for glycemic control in diabetes, *Diabetes Care*, **26**(4): 1277–1294.
- Yende S and van der Poll T (2009). Diabetes and sepsis outcomes--it is not all bad news, *Critical Care*, **13**(1): 117.
- Yeung G, Rawlinson WD and Craig ME (2011). Enterovirus infection and type 1 diabetes mellitus – A systematic review of molecular studies, *British Medical Journal*, **342**: d35
- Ylinen K, Aula P, Stenman U-H, Kesaniemi-Kuokkanen T and Teramo K (1984). Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy, *British Medical Journal*, **289**: 345–346.
- Yogev Y, R. C, Ben-Haroush A, Hod M and Bar J (2010). Maternal overweight and pregnancy outcome in women with Type-1 diabetes mellitus and different degrees of nephropathy, *Journal of Maternal Fetal & Neonatal Medicine*, **23**(9): 999–1003.
- Zgibor JC, Piatt GA, Ruppert K, Orchard TJ and Roberts MS (2006). Deficiencies of cardiovascular risk prediction models for type 1 diabetes, *Diabetes Care*, **29**(8): 1860–1865.
- Zgibor JC, Songer TJ, Kelsey SF, Drash AL and Orchard TJ (2002). Influence of health care providers on the development of diabetes complications: long-term follow-up from the Pittsburgh Epidemiology of Diabetes Complications Study, *Diabetes Care*, **25**(9): 1584–1590.
- Zgibor JC, Songer TJ, Kelsey SF, Weissfeld J, Drash AL, Becker D and Orchard TJ (2000). The association of diabetes specialist care with health care practices and glycemic control in patients with type 1 diabetes: a cross-sectional analysis from the Pittsburgh epidemiology of diabetes complications study, *Diabetes Care*, **23**(4): 472–476.
- Zhang A, Vertommen J, Van Gaal L and De Leeuw I (1995). Effects of pravastatin on lipid levels, in vitro oxidizability of non-HDL lipoproteins and microalbuminuria in IDDM patients, *Diabetes Research & Clinical Practice*, **29**(3): 189–194.
- Ziegler D, Hubinger A, Muhlen H and Gries FA (1992). Effects of previous glycaemic control on the onset and magnitude of cognitive dysfunction during hypoglycaemia in type 1 (insulin-dependent) diabetic patients, *Diabetologia*, **35**(9): 828–834.

Zipitis CS and Akobeng AK (2008). Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis, *Archives of Disease in Childhood*, **93**(6): 512–517.