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DIABETES STANDARD TREATMENT GUIDELINES

STANDARD TREATMENT GUIDELINES

FOR DIABETES

in TUVALU

SECOND EDITION 2012

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Diabetes standard treatment guidelines

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MANAGING DIABETES MELLITUS

Major drugs used in the management of diabetes and its complications

Drugs used in the management of diabetes

Biguanides

Metformin is the only drug of the biguanide group in the Tuvalu Essential Drug List (EDL).

Metformin reduces hepatic glucose output and insulin resistance. Metformin has been shown significantly reduce the risk of diabetes-related morbidity and mortality in overweight patients.

Used as a first-line drug in obese type 2 diabetics.

- -cleared from the body predominantly by renal excretion. It accumulates in renal impairment and should seldom be used in patients with serum creatinine more than 200mmol/L. Patients receiving longterm metformin should have 6-monthly monitoring of renal function.
- can cause lactic acidosis in situations such as ischemic heart disease, congestive heart failure Should be stopped for 48 hours before surgery or and renal impairment. administration of contrast radiography and only resumed once urine output and renal function have returned fully to normal. Hence, renal impairment contraindication to metformin.
- -no risk of hypoglycaemia when used alone.
- -major adverse effects: anorexia, nausea, abdominal discomfort and diarrhoea.

Metformin is given orally 2-3 times a day and taken with or after meals. The dose ranges from 500 mg BD to a maximum of 3 g/day in divided doses. Most physicians limit the dose to 2g daily because at higher doses, gastrointestinal side effects are more common.

Sulphonylureas

Glibenclamide is available on the Tuvalu Essential Medicine List.

- -acts on pancreatic beta-cells to induce insulin secretion.
- metabolized by the liver and predominantly cleared by the kidneys. Older patients and others with declining hepatic and renal function may be at risk of accumulation and hypoglycaemia.

-used in lean type 2 diabetics. Can be combined with metformin if diabetes control inadequate.

- -not recommended in pregnancy and lactating mothers.
- -hypoglycaemia the major adverse effect especially when there is significant hepatic and renal impairment.
- -dosage of glibenclamide varies from 2.5 mg to 20 mg daily orally with meals and in two divided doses above 10 mg up to a maximum of 20 mg/day.

Glipizide deleted from STG/EML and will no longer be available on the Tuvalu Essential Medicines List

- acts on pancreatic beta-cells to induce insulin secretions.
- metabolized by the liver and predominantly cleared by the kidneys. Older patients and others with declining hepatic and renal function may be at risk of accumulation and hypoglycaemia.
- used in type 2 diabetic. Can be combined with metformin if diabetes control inadequate.
- not recommended in pregnancy and lactating mothers.
- hypoglycaemia the major adverse effect especially when there is significant hepatic and renal impairment.
- dosage of glipizide varies from 2.5 to 40mg daily in 1 to 2 doses orally with meals.

Insulins

There are three insulin preparations available in the Tuvalu EML. In this section, the pharmacokinetics of these preparations is discussed. Their usage is discussed on pages16 & 16.

Insulin is given using conventional disposable insulin syringes.

The preferred sites of injection are the abdominal wall, the deltoids and the thighs. It is recommended that these sites be rotated regularly.

Table 1. Characteristics of available insulins.

Insulin Type	Effect onset (h)	Maxmum effect (h)	Duration (h)
Short-acting soluble insulin, 100u/ml (Actrapid HM)	0.5	2-5	6-8
Intermediate-acting isophane insulin, 100 u/ml (Protaphane)	1-2.5	4-12	16-24
Biphasic isophane insulin, 100u/ml (Mixtard)	0.5-1	2-12	16-24

Drugs for treating complications and coexisting conditions

Amitriptyline

This compound, used for the treatment of depression, is also of value in a variety of pain syndromes. It may play a role in modifying the activity of the descending, adrenergic pathway in the spinal cord – possibly by limiting the re-entry of catecholamines into the sympathetic nerve endings.

In doses for the relief of pain in diabetic neuropathy, the major adverse drug effects are dry mouth and blurring of vision.

-usual dose 50 to 75 mg at night.

Carbamazepine

Carbamazepine has a place in the treatment of several pain syndromes. The mode of action is unknown: good evidence exists from clinical trials to support its use. In the dose used for diabetic neuropathy, major adverse effects are less likely to occur. However, drowsiness, skin rash and slurred speech or mild ataxia should be looked for.

Angiotensin-converting enzyme inhibitors (ACEIs)

ACEIs play a vital role in the treatment of microalbuminuria and control of hypertension in diabetic patients. Enalapril is the only preparation available in the Tuvalu EML.

Classification, diagnosis and general management of diabetes

Types of diabetes

Type 1 diabetes

Previously known as insulin-dependent diabetes mellitus (IDDM), type 1 diabetes is caused by destruction of pancreatic beta-cells usually by autoimmune mechanism. Patients require life-long insulin treatment. Type 1 diabetes is commonly seen in young patients but can also be present in older patients. They have lean bodies and are prone to ketoacidosis.

Type 2 diabetes

Previously known as non-insulin dependent diabetes mellitus (NIDDM), type 2 diabetes is the commonest type seen in Tuvalu and is increasing worldwide. Onset usually later in life but recent epidemiologic studies show that there is increasing trend in younger patients. Type 2 diabetes is often associated with hypertension, hyperlipidaemia and truncal obesity. This is referred to as syndrome X or the "metabolic" syndrome..

in pancreatic insulin secretion, abnormal regulation of hepatic glucose Abnormalities production and tissue resistance to the action of insulin have all been demonstrated in Type 2 diabetes.

Patients with Type 2 diabetes commonly have a family history of the condition, are often over 40 years of age, often have a body mass index (BMI) over 25 kg/m², and may have history of gestational diabetes.

Sometimes, differentiating between the two types can be difficult. In such cases, an initial trial of oral hypoglycaemic agents can be given. If the response is unsatisfactory, then insulin therapy should be instituted.

Secondary diabetes

Secondary diabetes occurs in the following situations:

- endocrine disorders acromegaly, Cushing's disease, thyrotoxicosis and sometimes in phaeochromocytoma (an adrenal medullary tumour producing catecholamines in excess)
- during treatment with corticosteroids
- thiazide diuretic therapy (usually impaired glucose tolerance not full diabetes)
- pancreatic destruction due to surgery, cancer and chronic diseases of the pancreas.

Screening for diabetes

Early detection of diabetes in our population is vital in order to reduce the disease burden of diabetes in our community. A high index of suspicion in certain categories of the population is important. However, the definitive diagnosis is based on the blood sugar levels.

One should suspect diabetes in the following categories of patients:

Patients at risk

- positive family history
- hyperlipidemia
- hypertension
- 40 years old
- obesity
- history of gestational diabetes

Patients with typical symptoms of diabetes have -

- weight loss
- polyuria
- lethargy
- pruritus vulvae
- balanitis

Patients suffering from conditions suggestive of diabetes

- foot sepsis
- multiple abscesses
- delayed wound healing
- neuropath

Diagnosis of diabetes mellitus

A three-step screening and diagnosis procedure is recommended for detecting undiagnosed type 2 diabetes:

1. Initial risk assessment using a risk assessment tool or risk factors

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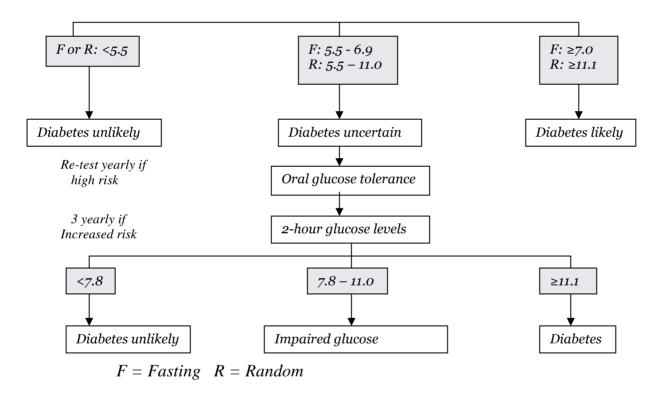
- Measurement of fasting plasma glucose
- Sometimes an oral glucose tolerance test (OGTT).

Diagnosis must be confirmed on subsequent day unless unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms are present.

The OGTT is unnecessary to diagnose diabetes in people with an unequivocally elevated fasting or random plasma glucose. An OGTT needs to be performed in a person with an equivocal result (see Fig.1)

The test is carried out after an overnight fast, following three days of adequate carbohydrate intake (greater than 150g per day). A 75g load of oral glucose is given and the diagnosis of diabetes can be made if venous plasma glucose level fasting is 7.0 mmol/L or 2-hour post glucose load is 11.1 mmol/L.

Figure 1. Glucose levels - venous plasma:mmol/L



Impaired fasting glycaemia and impaired glucose tolerance

Impaired fasting glycaemia (IFT) and impaired glucose tolerance (IGT) are both regarded as pre-diabetic states. Patients identified by screening should be reviewed by a medical practitioner, advised to follow an appropriate diet and then followed up at 6 months with further measurements of fasting and 2-hour postprandial blood sugars. About 30% of pre-diabetic patients develop overt diabetes in five years.

Management of established diabetes

Diabetes mellitus is a complex disease to treat, and as such, it needs a holistic approach in its management.

There should be an **explicit management plan** to include:

- adequate blood glucose control food intake, weight control, physical activity and drug therapy;
- risk factor modification particularly hypertension, obesity, smoking and hyperlipidemia;
- screening and management of complications;
- regular follow-up; and

1

• a comprehensive and repeated educational program.

The aims of treatment for diabetes are to relieve symptoms of the disease:

- to avoid immediate complications (i.e. hypoglycemia and hyperglycemia), and
- to delay the onset of long-term complications (i.e. retinopathy, neuropathy, nephropathy,
- and cardiovascular diseases).

There is good evidence that very good long-term control of blood glucose reduces the likelihood of development of microvascular complications of diabetes.

Adequate blood sugar control

Blood sugar control is affected by five factors such as:

- food intake,
- physical activity,
- stress, and
- drug treatment
- co-existing medical conditions

Food intake a.

All newly diagnosed patients should be referred to a dietician or in the outer islands to be counseled using materials provided in the appendix section.

Diet should include plenty of breads, cereals, vegetables and fruits, moderate amounts of low- fat meat, poultry, fish, eggs and dairy products and only a small intake of foods high in fats, added sugar and salt.

A dietitian will be able to point out ways in which variety may be achieved without losing control of the blood glucose. Avoidance of sugar in the diet alone is not an adequate dietary measure.

Patients with Type 1 diabetes must eat regularly to avoid hypoglycemia due to insulin therapy.

Artificial sweeteners such as saccharine and cyclamate can be used as substitutes. Sorbitol should not be used as a sweetener.

Alcohol should be no more than two standard drinks daily. There is a risk of severe hypoglycaemia if excessive alcohol is consumed. Alcohol should be taken with a meal and not by itself.

The effects of yaqona are unclear. Prolonged drinking sessions may lead to missing meals. There is anecdotal evidence that yaqona may have hyperglycemic effects.

b. Weight control

Many Type 2 diabetics are overweight. They should be encouraged to achieve as close as possible to their ideal body weight (BMI between 20 to 25 kg/m²). This will also assist in the control of hyperlipidemia

¹ One standard alcohol drink is equivalent to 10 g of alcohol (285 ml of regular beer, 100 ml of wine, and 30 ml of spirits).

c. Physical activity

Physical activity is important for all diabetics and can assist in weight reduction and improve cardiovascular fitness. The common health goal should be to achieve at least 30 minutes of moderateintensity physical activity every day. This includes activities such as brisk walking, cycling, and physical work. Additional health benefits can be obtained by more vigorous activities (such as dancing or jogging,) or through longer duration moderate-intensity activities.

d. **Drug therapy**

Drug treatment of diabetes modifies the tissue production of glucose or its uptake from the blood into cells.

Risk factor modification

a. **Smoking**

Diabetics should not smoke.

b. Hypertension

-a major risk factor for both cardiovascular diseases and renal complications.

Blood pressure control is more important than the choice of anti-hypertensive drugs. However, angiotensin converting enzyme inhibitors (ACEIs) are the first line drugs in controlling hypertension. Other anti-hypertensive drugs such as beta-blockers (e.g. atenolol) and slow release calcium channel blockers (e.g. nifedipine), can also be used. Methyldopa is available and, while usually reserved for controlling blood pressure in pregnancy, can be used if the above drugs are not available. combination of drugs is often needed to achieve desired blood pressure control.

When ACEIs are used to control hypertension, it is important to monitor the renal function two weeks later. A slight increase in serum creatinine is generally expected and is usually less than 30% of baseline values. If there is a significant rise in serum creatinine, it is recommended that ACEIs should be stopped and replaced by another anti-hypertensive drug. This might indicate underlying renal artery stenosis.

The level of blood pressure control is dependent on the patient's renal function and the amount of protein in the urine. Targets are :-

- If renal function is normal (regardless of blood pressure) but microalbuminuria is present, start enalapril 5-40 mg daily. The target of BP control is less than 130/85 mm Hg.
- In the presence of renal impairment and/or significant proteinuria (>1 g/day or ii. ++++ on dipstick), the BP should be lower than 120/80 mm Hg.

Caution is required with ACEIs therapy because of the risk of development of hyperkalemia. When possible, it is advisable to monitor electrolytes at least once every six months. Regular monitoring of electrolytes is advisable.

Hyperlipidemia c.

This is a common occurrence in diabetics.

Elevated triglycerides and LDL (low-density lipoprotein)-cholesterol with reduced HDL (high density lipoprotein)-cholesterol is a common pattern and warrants treatment.

Getting the best possible control of blood glucose is an important first strategy.

If lipid abnormalities persist despite this, they may need to be treated in their own right. The recommended drug is simvastatin,

Tablet 2 Goals for optimum diabetes management

Encourage all people with diabetes to reach these goals			
BGL	Ideal 4.0-6.0 mmol/L (fasting)		
	NHMRC 6.1-8.0 mmol/L (fasting)		
HbA1c	7%		
LDL – C	<2.5 mmol/L		
Total Cholesterol	$<4.0 \ mmol/L$		
HDL-C	>1.0 mmol/L		
Triglycerides	<1.5 mmol/L		
Blood pressure	130/80 mm Hg		
BMI	<25kg/m² where appropriate		
Urinary albumin excretion	<20µg/min (timed overnight collection)		
	<20mg/L (spot collection)		
	<3.5mg/mmol: women		
	<2.5mg/mmol: men (albumin creatinine ration)		
Cigarette consumption	Zero		
Alcohol intake	2 standard drinks (20g) per day for men and women		
Physical activity	At least 30 minutes walking (or equivalent) 5 or more		
	days/week.		
	(Total 150 minutes/week)		

Doctors should consider:

- Prophylactic aspirin (75-325mg) daily unless contraindication
- Immunisation against influenza and pneumococcal disease

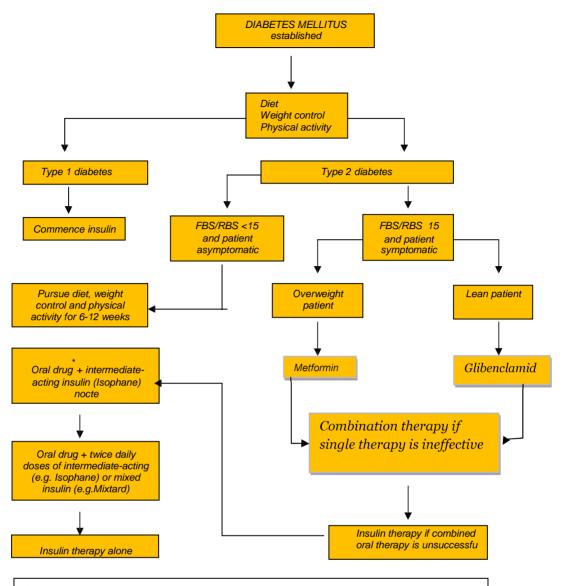
Specific aspects in the management of diabetes

General approach to the management of diabetes

The general approach to the management of diabetes is outlined in Figure 1.

For all diabetics, diet, weight control and regular physical activity are essential. regimens can produce good glucose control in type 2 diabetes; and if it does, then these should Drug therapy should only be considered if blood sugar levels remain be pursued. uncontrolled after 6-12 weeks.

The discussion below refers to those patients whose blood sugar levels are not adequately controlled with non-pharmacological therapy



*Metformin is preferable over sulfonylureas.

Figure 2. General approach to the management of diabetes mellitus.

Type 1 diabetes

All patients with Type 1 diabetes require insulin.

Children should be referred to a specialist paediatric unit and will normally be stabilised in hospital. Adults can be managed as an outpatient.

Insulin dose has to be worked out for each individual according to blood glucose control.

Type 2 diabetes

Obese patients (BMI > 30 kg/m^2)

For obese type 2 diabetic patients, start on

Metformin 500 mg orally 2-3 times daily up to a maximum of 2 g daily with meals.

If blood sugar levels are uncontrolled, add glibenclamide (see below). Add insulin if still not controlled.

Non-obese type 2 diabetes

For non-obese type 2 diabetic, start on

Glibenclamide 2.5 to 10 mg as a single dose or twice daily up to a maximum of 20 mg meals or after meals. This drug is preferred in younger patients.

Combination oral treatment

If blood sugar is not adequately controlled with a single oral agent, give

Metformin + glibenclamide (doses as above).

Insulin treatment in type 2 diabetes

Deciding when to start a.

The indications to start insulin in type 2 diabetes are:-

- failure of oral hypoglycaemic agents,
- patients undergoing major surgery
- critically ill patients, pregnancy

b. Administering insulin with oral hypoglycaemic drugs

- Intermediate-acting isophane 10 units subcutaneously at bedtime and adjust dose according to blood sugar levels OR
- Intermediate-acting isophane insulin OR
- mixed insulin 8-10 units subcutaneously twice daily with subsequent adjustment of the dose according to blood glucose levels.

Insulin regimens² C.

i. Multiple-dose ("QID") regimen

This regimen is more suited for stabilization of blood sugar for inpatients.

Soluble insulin starting with 5 units subcutaneously 30 minutes before each meal

AND

Intermediate-acting isophane 8 units subcutaneously at bedtime.

Insulin doses should be adjusted based on blood sugar levels.

Twice daily regimen (Refer also to Insulin Commencement & **Titration Order)**

This regimen can be used for control of blood sugar for both inpatients and outpatients.

Intermediate-acting isophane insulin 10 units in the morning and 5 units in the evening subcutaneously 30 minutes before each meal.

OR

Mixed insulin 10 units in the morning and 5 units in the evening subcutaneously 30 minutes before each meal.

In principle, two-thirds of the insulin dose should be administered in the morning and one-thirds in the evening. However, insulin doses should be adjusted based on the blood sugar levels and increments of 2 units per dose are recommended.

Special situations in the management of diabetes

² For both insulin regimens, extra soluble insulin 5 units subcutaneously can be given if blood sugars are not controlled.

Physical Activity

Physical activity carries additional risks in people with diabetes requiring insulin. Hypoglycaemia is a major concern in this situation.

For mild to moderate physical activity (e.g. fast walking on a flat surface, mopping the floor) for 30 minutes, extra carbohydrates should be taken beforehand.

For "short bursts" or longer hard physical activity (e.g. scrubbing the floor, moving heavy furniture), it is advisable to reduce dosage of short-acting insulin.

Illness

Metabolic control may deteriorate rapidly during illness of any kind.

As part of their education program all patients should have a contingency plan on which they can work on if an illness upsets their diabetes control.

There should be close monitoring of blood sugar levels.

Insulin doses should be adjusted according to blood sugar levels and changed to short- acting insulin for better control. Insulin must not be stopped. If there is a need to reduce the dose, it should not be more than 30%.

Oral hypoglycaemic drugs should not be stopped unless the patient cannot eat. Maintenance of fluid intake is important.

If the patient is unable to take in solid food, substitute with fruit juices, regular soft drinks, or other fluids containing glucose.

Patients who have repeated vomiting should contact medical help early as both intake of fluids and carbohydrates need to be maintained.

The patient should have thorough knowledge of when, how and where to contact a specialist health care facility.

Travelling

Patients on insulin can travel overseas as long there is proper adjustment of their food and insulin doses to adapt to the changing local times.

Journeys should be carefully planned. Enough insulin for the whole trip with some spares should be carried. Insulin should be kept cool inside a well-insulated bag. It is advisable to carry a medical report from the doctor with treatment details to facilitate customs clearance. The report will assist in dealing with any medical problems that may arise during traveling.

Easily absorbed sugary foods (e.g. lollies, fruit juice) should be available while traveling as well as food that takes a little longer (e.g. crackers) to absorb. These can be taken if there is an indication of impending hypoglycaemia.

Surgical procedures

The major issues in patients undergoing surgical procedures are the following:

the need to fast the patient,

the need to maintain glycaemic control throughout the procedure,

the need to avoid hypoglycaemia, and

the need to shift from a rigid preoperative regimen to a very flexible perioperative regimen.

It is desirable for the patient to have normal blood sugar levels and maintenance of fluid and electrolyte balance perioperatively.

Local anaesthesia

Patients with normal blood sugar levels a.

There is no need to fast patients prior to surgery and the normal doses of insulin or oral hypoglycaemic drugs should be continued. Do a morning preoperative blood sugar reading. Dextrose 5% may be given if the blood sugar is low.

b. Patients with uncontrolled blood sugar levels

Control blood sugar levels first and refer to physician if required. Plan surgery once blood sugar is controlled.

General anaesthesia

a. Patients for elective surgery

Preoperative blood sugar levels should be controlled with either oral hypoglycaemic agents or insulin.

i. Patients on oral hypoglycaemic agents

It is recommended to admit patient 2-3 days before surgery and change from oral hypoglycaemic drugs to insulin. Stabilize blood sugar levels using multiple-dose ("QID") insulin regimen. Give extra soluble insulin 5-10 units subcutaneously if the blood sugar level is 12 mmol/L.

ii. Patients on insulin therapy

It is recommended that patients be admitted a day before surgery and be started on multiple-dose ("OID") insulin regimen. Give extra soluble insulin units subcutaneously if the blood sugar level is 12 mmol/L.

On the day of surgery, omit the morning dose of insulin. Check blood sugar level to ensure that diabetes is under control. The patient might require glucose- insulinpotassium (GIP) infusion depending on the surgery schedule.

Glucose-insulin-potassium (GIP) infusion:

One liter of 5% dextrose + 20 units of soluble insulin +20 mmol of potassium chloride, to run for 100 ml/hr.

iii. During induction of anaesthesia and surgery

Close monitoring will be done by the anaesthetist.

iv. **Postoperative**

Insulin therapy is continued till the wound is healing satisfactorily. By this time, the patient can be changed to the usual oral hypoglycaemic drug or insulin therapy.

b. Patients for emergency surgery

Start insulin infusion and monitor blood sugar levels according to protocol in the Appendix.

While principles remain the same as in adults, management of children with diabetes should be undertaken by a specialist paediatrician.

Management of acute complications of diabetes

Hypoglycaemia

Hypoglycaemia presents as:

sweating, tremor, tachycardia and pallor from adrenal and sympathetic activity triggered by the

low blood glucose and/or hunger, mental confusion, coma and seizures.

The factors that precipitate hypoglycaemia include:

- high insulin dose,
- high doses of sulphonylureas,
- presence of renal failure,
- liver disorder,
- septicaemia,
- missed meals,
- hormonal disturbances, and
- vigorous physical activity.

Patients should be treated urgently.

If the patient is conscious and able to swallow, give a sugary food or drink followed by foods that are absorbed longer, e.g. crackers.

If the patient is unable to swallow or unconscious at home, give sugar paste or honey into the mouth and transfer immediately to the nearest health care facility for intravenous glucose therapy. At the health care facility, if the patient unconscious or unable to swallow:

50% 50 ml intravenously followed by continuous Give dextrose intravenous infusion of 5% dextrose for up to 24 hours.

Hypoglycaemia in the elderly, particularly as a consequence of accumulation of sulphonylurea in the plasma, may be difficult to reverse and may reoccur for several days after stopping the drug.

HYPERGLYCEMIC EMERGENCY

Diabetic ketoacidosis (DKA)

What is Diabetic ketoacidosis?

- It is an absolute insulin deficiency results in:
 - -increasing hepatic glucose production
 - -osmotic diuresis and dehydration, potassium and phosphate depletion
- Increasing peripheral lipolysis. The liver, in the absence of insulin, converts fatty acids into ketoacids which cause the acidosis.

Pathophysiology

Hyperglycemia due to:

increase gluconeogenesis increase glycogenolysis decrease glucose uptake into cells

Ketosis due to: inability to utilize glucose- mobilisation and oxidation of fatty acids- ketogenesis-decrease ketone clearance

Precipitants

- Failure to comply with insulin therapy
- Infection i.e pneumonia, UTI, Cholecystitis
- Ischemia or Infarction
- Intoxication (alcohol, drugs)
- Iatrogenesis (glucorcorticoids, thiazides)

Clinical Manifestations

- Polyuria, Polydipsia, and Dehydration
- Dehydration- Inc HR, hypotension, dry mucosal memebranes, dec skin turgor
- Nausea, vommitting, abdominal pain, ileus
- Kussmauls respiration(deep) to compensate for metabolic acidosis,
- Ketotic breath (acetone) odor
- Mental confusion progressing to coma

Effects on vital signs that are related to DKA

- Tachycardia
- Hypotension
- Tachypnea
- Hypothermia
- Fever, if infection is present

Specific signs of DKA may include the following:

- Confusion
- Coma

Abdominal tenderness

DKA might be the first presentation in an unknown type 1 diabetic.

The common precipitating factors of DKA include:

- history of omission of insulin;
- drugs, e.g.corticosteroids;
- sepsis;
- acute coronary event;
- recent trauma; and
- pregnancy.

DIAGNOSTIC STUDY

- Initial investigations- blood glucose, arterial blood gases,
- electrolytes and renal function,
- urine, glucose, ketones, microscopy and culture
- **ECG**
- Chest Xray

FREQUEST OBSERVATION

- Clinical and biochemical status
- Hourly- BP, Pulse, Urine Output, Capillary blood glucose
- 2 hourly- electrolytes especially potassium

FLUID REPLACEMENT

Adults:

- Correction of fluid loss with intravenous fluids preferably NS
- -1L for the 1st 30minutes
- -1L for the 1 hour
- -1L for 2 hrs
- -1L for 4 hrs

Further infusion should be administered according to clinical assessment

Paediatrics:

- Fluids needed calculated as 40-80mls/kg (Deficit)
- Calculate deficit plus continuing requirements for the next 24 hrs
- Give about 1/3 of this in the 1st 5-6 hours
- Normal saline is suitable

INSULIN THERAPY

- IV bolus dose of 10units short acting insulin followed by
- 4units/hour of short acting insulin either by direct IV administration or by using an infusion pump if one is available
- Measure blood sugar level every hour and insulin dose adjusted
- Once blood sugar is <12mmol/L, then give 2units/hr
- If blood sugar is controlled after a few hours, then insulin regimen can be changed to multi dose (QID) regimen sub cut followed by twice daily dosing.

- A safe and cautious approach is to start supplementary intravenous potassium at a rate of no more than 10-20mmol/hr once insulin and fluids have been started and when renal function and urinary output have been assessed as satisfactory.
- Measure potassium level after 2 hours
- Bicarbonate- sodium bicarbonate should not be given routinely unless Ph is <7. infuse 50mmol of sodium bicarb over an hour

Treatment of Underlying cause

- Treat the underlying cause especially infection
- Other measures
- IDC for urine output mornitoring
- Oxygen therapy and insertion of NG tube if needed
- Counsel patient once fully recovered

Management

Management should be undertaken urgently in the nearest health care facility.

a. Fluids

Administer intravenous infusion of normal saline as follows:

One liter for 30 minutes One liter for one hour One liter for 2 hours One liter for 4 hours

Further infusion should be administered according to clinical assessment of the patient. In children, a paediatrician should be consulted and appropriate fluid management should be administered.

Once the blood sugar is 12 mmol/L, change intravenous fluid to either dextrose saline or dextrose 5%.

Insulin b.

Intravenous bolus dose of 10 units short-acting insulin followed by short- acting insulin intravenously 4 units/hour either by direct intravenous administration or by using an infusion pump if one is available.

If venous access cannot be established, give:

Short-acting insulin intramuscularly 8 units /hour.

Blood sugar should be measured every hour and insulin doses adjusted³. Insulin doses can be halved when blood glucose reaches 12 mmol/l. Thereafter, insulin can be change to multiple-dose ("QID") insulin regimen

subcutaneously followed by twice-daily dosing.

If infusion pumps are not available use the microset intravenous giving set used in paediatrics to achieve the required infusion rate.

c. **Electrolytes**

i. Potassium

Insulin takes glucose and potassium into the cells and their serum concentrations fall. Give potassium supplement of no more that 10-20mmol/hour once insulin and fluids have been started and when renal function and urinary output have been assessed as satisfactory.

Measure serum potassium along with serum sodium every 4-6 hours.

ii. **Bicarbonate**

Sodium bicarbonate should not be given routinely. It is only given when the blood pH is less than 7.0. In such cases, infuse 50 mmol of sodium bicarbonate over one hour.

c. Treatment of underlying cause

Treat the underlying cause especially infections and counsel patient and relatives of the outcome.

d. Other measures

³ For adjustment of doses of insulin infusion, refer to the appendix.

An indwelling catheter should be inserted to monitor urine output. Other measures that may be required are: oxygen therapy and insertion of nasogastric tube if paralytic ileus develops.

On recovery, every patient with DKA should be re-educated about avoidance of the complication and the recognition of early warning signs and symptoms.

Special considerations in children (but always contact a paediatrician)

Rehydration is critical. The degree of dehydration should be assessed as follows:

Mild (3% or less) - just clinically detectable. Moderate (around 6%) - easily detected, reduced skin turgor, poor capillary

Severe (10%) - poor perfusion, rapid pulse, reduced blood pressure.

Normal saline is the recommended intravenous fluid for rehydration.

Deficits should be replaced gradually (over 24-48 hours) and **not with rapid infusion** as is appropriate for adults. Tables are available to guide the rate of fluid replacement according to body weight and degree of dehydration.

HYPEROSMOLAR AND NON KETOTIC COMA (HNKC)

Features of HNKC

- Extreme hyperglycemia -develops because of increased hepatic glucose production and decreased peripheral glucose utilisation and also because of the fluid loss caused by the osmotic diuresis causing profound Dehydration
- Liposis and ketosis are not major features of Hyperosmolar non ketotic coma

Diagnostic studies

Initial investigations and Observations are similar to those of DKA

Fluids and Electrolytes

- Most patients have a deficit of many liters (60- 100ml/kg).
- The priority is to correct extracellular fluid volume and then slowly correct the hyperglycemia with insulin and water deficit with low sodium fluids.
- Initially normal saline is suitable to replete the extracellular vol, low sodium fluids will be required after

Electrolytes

- As long as the potassium is not very high (eg >5mmol/L) start replacement (0.5-1gm), measure levels and adjust the dose at least 2 hourly
- Insulin- same as DKA
- Once blood glucose level falls below 15mmol/L set up a 5% dextrose infusion 50-100ml per hour

TREATMENT OF OTHER CONDITION ASSOCIATED WITH DIABETES

- Neuropathy usually peripheral neuropathy
- - amitriptyline 50- 150mg NOCTE or Carbamazepine 600mg orally daily in 2 divided doses usually starts at 100mg daily then slowly increasing to the max dose of 600mg
- Infections
- Skin infections ie foot sepsis
- Cloxacillin plus metronidazole

Management of late complications of diabetes

Retinopathy

Diabetic retinopathy is a major cause of blindness. Retinopathic lesions are divided mainly into two categories: background and proliferative retinopathy.

Visual acuity and fundoscopic examination (if possible) with pupillary dilation should be carried out every year and more often if there is evidence of retinopathy. Specialist ophthalmological opinion and early treatment of lesions (i.e. by laser beam) may be required if it is available.

It is preferable that all diabetics are assessed initially by an ophthalmologist.

Good diabetic control is essential to reduce progression of the retinopathy and/or other complications such as nephropathy and neuropathy.

Neuropathy

Several different types of neuropathy can develop in diabetic patients. The commonly seen ones are peripheral sensory-motor and autonomic neuropathy.

Peripheral sensory-motor neuropathy

Symptoms of peripheral sensory-motor neuropathy include:

- numbness,
- paresthaesia,
- pain, and
- weakness.

If pain is prominent, several treatments have been shown to be effective.

Amitriptyline 50-150 mg orally at bedtime OR

Carbamazepine up to 600 mg orally daily in two divided doses.

plus

Vitamin B complex – one tablet daily

Carbamazepine should be introduced gradually starting at 100 mg twice daily and the dose to be increased gradually until the maximum dose that can control the pain can be achieved.

Good glycaemic control is essential for control of symptoms.

Autonomic neuropathy

Chapter: Foot infections

Autonomic neuropathy can present as:

- postural hypotension,
- dysphagia,
- intermittent diarrhoea,
- impotence,
- bladder atony.

Postural hypotension requires specialist assessment but the patient may respond to:

Fludrocortisone 100-300 g orally daily

Fludrocortisone is not available in the Tuvalu Essential Medicines.

Foot infections

DIABETIC FOOT SEPSIS

Diabetic foot sepsis is a serious infection and should be treated as an emergency. The outcome depends on the initial management of the sepsis and blood sugar control. Delay in treatment and or the inadequate initial treatment may result in the loss of the feet, the limb or life.

The appearance of the infected limb may be deceiving, as there is usually involvement of muscle and bone.

Step 1: Feel for the peripheral pulses (dorsalis pedes and posterior tibial arteries).

Peripheral pulses present:

Is wound discharging and/or foul smelling;

Start IV Cloxacillin, Crystaline penicillin and

Flagyl IV Normal Saline to correct dehydration

Start insulin for sugar control

Foot X-Ray to rule out osteomyelitis / foreign body

Urgent Surgical Debridement, done under tourniquet. (all dead tissue and tissue that is questionable, including bone is excised, peroxide washed and dressed with peroxide/saline mixture)

Peripheral Pulse Present:

Wound is not discharging and not foul smelling;

Start oral cloxacillin

Normal Saline dressing (no surgical debridement need)

Sugar control with oral hypoglycaemic.

(Monitor wound daily and watch for discharge and or bad smell. May need skin grafting if wound is large)

Peripheral Pulses Not Present:

Wound is smelling

Start IV Cloxacillin and Flagyl

Saline Dressing

Control Blood Sugar

Refer for Major limb Amputation

Peripheral Pulses Not Present:

Wound is dry and not smelling

Start oral cloxacillin

Apply dry dressing

Refer for major limb amputation

FOOT CARE

Foot care - refer to FOOT CARE POSTER

Nephropathy

Diabetic nephropathy usually takes 10-15 years to develop after the onset of hyperglycemia and it encompasses all the lesions occurring in the kidneys of patients with diabetes mellitus. Microalbuminuria is the earliest manifestation of diabetic nephropathy and is a marker of progressive deterioration of renal function. Yearly assessment of renal function is important. The literature recommends treatment with angiotension converting enzyme inhibitors (ACEIs) once microalbuminuria is detected. This test is not available in Tuvalu. USE

Enalapril 2.5-5 mg daily.

In general, treatment of established diabetic nephropathy includes the following:

- control of protein intake,
- use of ACEIs to reduce proteinuria,
- control of blood pressure,
- meticulous control of hyperglycaemia,

- control of hyperlipidaemia, and
- control of other vascular risk factors, i.e cessation of smoking.

For details of control of blood pressure and hyperlipidaemia, refer to cardiovascular guidelines Good blood pressure control as well as good glucose control is essential in all diabetics to reduce progression of complications.

Diabetes in pregnancy

Most diabetics can expect to have a successful outcome to a pregnancy. Foetal malformations are common in women who have poor diabetic control in the first trimester. Macrosomia (a big, "chubby" baby) occurs in women with poor control in mid- to late pregnancy.

Pre-eclampsia, hydramnios and peripartum complications are all common in diabetics. After birth, babies must be monitored for hypoglycaemia.

Pre-conception clinics

Ideally, diabetic women should have the opportunity to be assessed and counseled during pre-conception clinics before deciding on pregnancy.

More often, women present in the late first trimester, or even as an emergency when they are already in labour. By then, it will be too late to assess and manage their diabetic state.

Management of pre-existing diabetes in pregnancy

The cardinal points to emphasize are:

- adequate control of blood sugar levels,
- proper nutrition, and
- moderate physical activity.

Control of blood sugar levels

Multiple-dose ("QID") insulin regimen consisting of short-acting insulin before main meals plus intermediate-acting isophane insulin at bedtime.

If there is a reluctance to undertake this, diabetes may be controlled with:

Mixed insulin twice daily; dose determined by blood glucose measurement

The **aims** of treatment are:

fasting blood sugar level of <5 mmol/L, 2-hour post-prandial blood sugar level <7 mmol/L, and pre-meal blood sugar level of <6 mmol/L.

Nutrition

All pregnant diabetics should review their diet with the assistance of a dietitian. Weight gain in pregnancy should be limited to 10-12 kg if possible.

Physical activity

Moderate physical activity should be continued into pregnancy.

A specialist physician working with the obstetrician should supervise the management of a pregnant diabetic. A paediatrician should assess the newborn child.

Gestational diabetes

This is defined as glucose intolerance first developing, or first detected, in pregnancy. It occurs in 1 in 20 pregnancies and seems particularly prevalent in Indian populations. Older women (over 30 years of age), the obese and those with a family history of diabetes are more likely to get gestational diabetes than others.

The condition is most likely to appear in the second trimester and will resolve spontaneously after delivery.

Screening for gestational diabetes

Several national diabetes associations recommend that screening should be performed in all pregnant women around 26 weeks of gestation.

Testing should be done as early as possible when there is:

- glycosuria at ante-natal clinic (renal threshold for glucose may fall in pregnancy);
- history of stillbirth;
- history of very large babies; and
- positive family history.

A formal oral glucose tolerance test in a fasting patient gives the most accurate results. Fasting blood sugar >5.5 mmol/L and 2-hour post-prandial blood sugar'8 mmol/L are diagnostic of gestational diabetes. As glucose tolerance test (GTT) is time-consuming, it is used only to confirm diagnosis.

For screening of antenatal mothers, a non-fasting oral glucose challenge is useful. Give an oral glucose load of 50-75 g to the non-fasting patient and measure blood sugar at one hour. If the blood sugar is 8 mmol/L, the result is suggestive of gestational diabetes but

further formal testing with a fasting oral glucose challenge should be done for However, blood sugar of '10mmol/L at one hour is diagnostic of gestational diabetes. confirmation.

Management of gestational diabetes

Gestational diabetes can nearly always be managed by diet alone and a dietitian's help should be sought. The same target of blood sugar levels in established non-diabetics are appropriate for gestational diabetes (see above).

Approximately, 10% of women with gestational diabetes may need treatment with insulin to achieve target blood sugar level. This treatment is important for foetal development and to avoid the complications of late pregnancy.

Many women are reluctant to accept the need for insulin - even short-term (insulin can almost invariably be discontinued after delivery as the metabolic disorder resolves very quickly). The closest control can be achieved with:

Short-acting insulin, 5 units subcutaneously three times daily ahead of main meals with close monitoring of blood glucose. Intermediate-acting insulin may not be required overnight.

If there is a reluctance to undertake this regimen, gestational diabetes may be controlled with:

Mixed insulin twice daily; dose determined by blood glucose measurement.

Management of diabetes during labour

Protocols exist in all maternity units.

Normally the patient will be known to the obstetric team and will have had antenatal care provided by them.

The aims of management are to:

- maintain normoglycaemia
- prevent complications both intra- and post-partum
- deliver a live infant.

Measure blood glucose hourly during labour

Administer the glucose-insulin-potassium intravenous regimen for:

- any patient who has already had a blood glucose exceeding 10 mmol/L in early labour;
- who is normally on more than 30 units of insulin daily; and
- patients exceeding a blood glucose of 10 mmol/L at a later stage in labour.
- The infusion contains 20 units of short-acting insulin and 20 mmol potassium chloride in each litre of 5% dextrose (glucose) and should be run at 100 ml/hour.

Blood glucose should be measured hourly during labour. This should be supplemented with:

Stat doses of short-acting insulin of 5 units, subcutaneously if blood glucose exceeds 12 mmol/L or 10 units if blood glucose exceeds 15 mmol/L.

The monitoring of blood glucose is less critical after delivery. Blood glucose may be monitored four-hourly for 24 hours after delivery and less frequently thereafter. Continue glucose/potassium /insulin drip for at least 12 hours after delivery.

As normal feeding resumes insulin can be adjusted to 8-hourly blood glucose measurements.

Insulin requirements usually fall rapidly in the post-partum period.

Insulin will not normally be required post-partum for patients with gestational diabetes.

After delivery

Women with gestational diabetes should be followed up with an oral glucose tolerance test about 6 week's postpartum. They are at risk of developing diabetes in later years and it is better to introduce some form of regular surveillance than encounter them with established diabetes (with or without irreversible complications) in later life.

SLIDING SCALE

Insulin commencement and titration order

If FBS is more than 8mmol/L and patient on maximum oral hypoglycaemic agents (eg metformin 500mg 2 BD and glibenclamide 5mg 2 BD) and there is no intercurrent illness (eg infection).

Basal insulin is needed when:

- FBS is more than 8mmol/L
- Maximum oral hypoglycaemic agents prescribed AND taken
- No intercurrent illness

Start with 10 units Isophane insulin at bedtime and titrate twice weekly

10 Units Isophane at bedtime			
Adjust twice weekly			
Mean fasting glucose	Insulin increase (units)		
(preceding 2 days)	(Ginico)		
> 10 mmol/l	8		
8 – 10.0 mmol/L	6		
7 – 7.9 mmol/L	4		
6 – 6.9 mmol/L	2		

Exceptions are,

- no increase in dosage if BGL <4 mmol/L in the preceding week
- no increase and small insulin dose decreases (2-4 Units) if severe hypoglycaemia (requiring assistance) or BGL <3.0 mmol/L in the preceding week.

Adapted from: Diabetes Care(2004), 26 (11), November, pp. 3080 – 86

Please start Isophane insuli	n 10 units at bedtime and titrate	
to a FBS of	_mmol/L	
arrange for medical review i	n diabetes clinic in	_months / weeks
NAME:		
SIGNATURE:		
DATE:		

Nutrition management involves controlling weight and the introduction of a healthy eating plan.

Healthy eating is a critical component in the management of type 1 and type 2 diabetes. In over 50% of people presenting with type 2 diabetes restriction of energy intake, increased activity and weight reduction will initially normalize blood glucose levels. Medication is likely to be needed later.

Maintaining cooperation during weight reduction can be a major problem. A consistent coordinated approach by the general practitioner, dietitian and diabetes educator helps the patient maintain the effort.

Nutritional Guidelines

While an appreciation of the diabetes by the general practitioner or physician is important, detailed instructions need to be given by a dietician. Constant reinforcement of dietary advice usually results in enhanced cooperation and better control.

Healthy eating, body weight and regular physical activity are important objectives in people with diabetes. The following criteria of 'overweight' apply to those of Pacific Islanders.

Body Mass Index

 $(BMI (kg/m^2) = weight (kilograms)$

Height squared (Metres ²)

The healthy BMI is 18.5 to 24.9, overweight 25 to 29.9, obese 30. As a rough guide the patient's healthy weight (kg) is approximately: Height (cm) -100.

Alternatively waist circumference (cm) can be used.

	Healthy	Overweight	Obese
Men	<94	94-101.9	102
Women	<80	80-87.9	88

Source: Diabetes Management in General Practice 2011/12

The key issue for a diet for a person with diabetes is the learning to eat a range of foods in amounts appropriate for energy requirements.

In people with type 2 diabetes increased activity and elimination of concentrated sources of energy with substitution with high fibre, carbohydrate foods will often bring the condition under control. Unless the patient is very symptomatic, a trial of at least 6 to 8 weeks of lifestyle modification is wise before oral hypoglycaemic agents are considered.

Body Weight

Loss of body weight will often result in near normal glycaemic, blood pressure and lipid profiles. Often an ideal body weight is not achievable and setting this as a goal discourages patients to attempt any dietary change. Many studies suggest that a weight loss of 5 to 20% will improve glycaemic control. Therefore it is important to encourage any degree of weight loss. A medium term goal for overweight patients is 5-10% body weight loss.

Sources of hidden energy need to be identified and minimized: for example alcohol, cakes and sweet beverages. A reduction

in total energy intake of 2,000 kilojoules (475 calories) per day should result in a weight loss of 0.5kg a week.

Carbohydrates

Carbohydrates foods which are rich in fibre and have a low energy density are the basis of the eating plan and it is recommended that they contribute up to 50% of the total energy intake. Meals containing carbohydrates are spread evenly through the day. Both the quantity of carbohydrate and the quality of carbohydrate will affect blood glucose levels. The amount of carbohydrate has a larger effect on glycaemia that the quality.

The quality of carbohydrate is reflected bby its glycaemic index (GI) which indicates the post prandial glycaemic response to a particular carbohydrate food. This will have a lesser but additional effect of blood glucose levels. The GI classifies carbohydrates as slow acting (low), moderate (medium) and quickly absorbed (high).

The glycaemic load (GL) refers to both the quantity and quality of carbohydrates. GL is the GI multiplied by the carbohydrate grams divided by 100. A low GL (less than 80GL per day) is desirable for people with diabetes. In practice it is recommended that people with diabetes have one high fibre, low GI carbohydrate food at each meal. This would include wholegrain breads, rolled oats, low fat low sugar breakfast cereals, pasta, beans, lentils and temperate fruits. Other carbohydrates foods can be included but in lesser amounts. These include rice, potato and tropical fruit.

Sugar does not need to be eliminated. Including a small amount of sugar as part of a mixed meal or food eg. Breakfast cereal, does not adversely affect the blood glucose level. Allowing small amounts of sugar as part of a high fibre, low fat meal plan increases the choice of foods available and may aid adherence.

Low carbohydrate, high protein diets may predispose the person to hypoglycaemia if they are taking sulphonyurea, repaglinide or insulin. Those adopting these diets should be made aware of the risk and the appropriate precautions.

Dietary fat

It is recommended that fat contribute to less than 30% of total energy intake. This has a beneficial effect on serum lipids and helps with weight reduction. Saturated fats in the diet will have an adverse effect on general lipid profiles.

The most common sources of oils and fats are:

- Additives in cooking
- 23 Dairy products
- Meat
- Snack and takeaway foods

Fried foods need to be avaioded (even with polyunsaturated or monosaturated oils).

Monosaturated fats (-6 polyunsaturated) lower LDL-C. Fish oils (-3 polyunsaturated oils) in doses of 5g/day lower triglyceride levels. They also inhibit platelet aggregation and may protect against thrombosis in diseased blood vessels.

THE MAIN THRUST OF MANAGEMENT IS TO LOWER TOTAL FAT INTAKE AND TO FIND SUBSTITUTES FOR SATURATED FATS.

Low fat milk could be used as a substitute for whole milk and some 'light' margarines have 40% of the fat content of standard margarines. Alternative spreads are reduced fat cottage cheese or ricotta cheese. Some margarines contain plant sterols that reduce cholesterol absorption and cholesterol levels.

There is considerable variation in the fat content of meats, depending on the source and cut. It is best to ask the butcher what is 'lean' and what is not, especially since the 'new cuts' are much lower in fat.

Dietary protein

It is recommended that protein contribute 10-20% of total energy. The types of proteins selection depends on the patient preferences taking into consideration that fat content of each source. Vegetable sources of proteins such as beans and pulses are very low in fat.

Alcohol

As many people with type 2 diabetes are overweight or obese, alcohol should **be minimised.** Low alcohol beers are a better choice than ordinary or diet beers.

Although small amounts of sugar can be included, alternative sweeteners may still have a role in management. Suitable sweeteners are deemed by the Food Standards Australia and New Zealand as suitable and safe for use in pregnancy, although some are known to cross the placenta. If concerned, pregnant women should speak to their health professional.

The inclusion of sugar alcohol, eg: sorbitol, is not recommended as these offer no advantage over sucrose in improving metabolic control, increasing cooperation or in managing weight loss.

APPENDIX 1

INSULIN INFUSION

Preparation

1. Infusion be electronic pump

99ml of normal saline in a chamber + 100 units (1ml) of short-acting (regular, soluble) insulin.

If infusion pump is not available, use insulin preparation as discussed under (2) below

2. Infusion by intravenous drip

1 liter of normal saline + 100 units (1ml) of short-acting (regular, soluble) insulin (concentration: 1 unit of insulin per 10 ml)

This preparation can be used either with ordinary intravenous set that is calibrated to provide macrodrops or the paediatric intravenous set providing microdrops.

1 ml = 15 macrodrops or 60 microdrops

Infusion Rate

Initially, give a bolus dose of 10 units of short-acting insulin IV and then infuse insulin continuously using either of the regimens shown below:

Capillary blood glucose	Infusion pump (ml/hr)		Intravenous dr 2	ip (Preparation
(CBG) (mmol/L)	Preparat ion (1)	Preparati on (2)	Macrodrops/	Microdrops/
	<u> </u>		min	min
< 6.0	0	0	0	0

6.0 - 10.0	4	40	10	40
10.1 - 14.0	6	60	15	60
14.1 - 18.0	8	80	20	80
18.1 - 22.0	10	100	25	100

Stat doses of short-acting insulin of 5 units intravenously if blood glucose exceeds 12 mmol/L or 10 units if blood glucose exceeds 15 mmol/L.

Serum potassium must be monitored during the infusion. If fluid restriction is essential, preparation (1) is recommended.

CASE STUDIES

Dr Sanson Fousaga

1. An inquisitive patient walked into your clinic and asked 'What are the two major forms of diabetes mellitus?' Please nurse can you differentiate between them???

True or false – Type 1 diabetes is also known as diabetes insipidus

- 2. True or False
- A 12 year old female was brought into ER complaining of polyuria, polydipsia and dehydration. She is tachycardia and her RBS was 25 mmol/L. Ketone stick tested postive. This is most likely diabetes mellitus type 2.
 - a. The most important blood glucose level to determine the status of diabetes mellitus is
 - b. Postprandial
 - c. Pre-prandial
 - d. Venous blood
- 3. It's your first day at work on Nui island when a 56 year old man greet you with a foul smell wound on her left big toe which has been there for 1 week. He said he does not have DM2. You take her RBS and it reads 24 mmol/L.

What questions do you need to ask this patient before further management??

- Does this patient has DM type 2?
- What is your normal range of RBS?
- What is your normal range of FBS?
- You weight him and calculated his BMI to 25. You know obesity is one of the risk factors of DM2. What are the other risk factors you should be able to determine in this case??

- 4. You have just started to work on Nukulaelae Island when a 47 year old woman was found to have a RBS of 12.3mmol/L. How would you manage this case???
- 5. After initial management of a 48yo male DM2, you called her in for review in the next 2 weeks? State a checklist for your nursing review on this patient.

AUALA E MAFAI O FAI KE TAUSI OU VAE





Aasi ou alofi – vae io me ko maikao vae

Fulu ke maa ou vae







Milimili ki se sinu io me se cream

Kati ou mania vae ke mutu fakalei





Fakaoga taka e tau ki te tau o aso i Tuvalu



NOTES	