

# 1 Drugs in diabetes<sup>1</sup>

This section contains brief summaries of the major drugs used in the management of diabetes and its complications. These summaries do not contain comprehensive accounts of the pharmacology of these compounds. The reader is advised to consult the manufacturer's product information or standard pharmacology textbooks for more details.

## 1.1 Drugs used in the management of diabetes

### 1.1.1 Biguanides

Metformin is the only drug of the biguanide group available on the Fiji Essential Drug List (EDL).

It lowers blood glucose by suppressing hepatic glucose production and increasing tissue sensitivity to insulin.

It is used as a first-line drug in obese type 2 diabetics.

It is 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 200  $\mu\text{mol/L}$ . Patients receiving long-term metformin should have regular (at least 6-monthly) monitoring of their renal function.

It is contraindicated in pregnancy and breastfeeding mothers.

It can cause **lactic acidosis** in situations such as ischemic heart disease, congestive heart failure and renal impairment. It should be stopped for 48 hours before surgery or administration of contrast radiography and only resumed once urine output and renal function have returned fully to normal.

There is no risk of hypoglycaemia when used alone.

Its major adverse effects are: anorexia, nausea, abdominal discomfort and diarrhoea.

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

### 1.1.2 Sulphonylureas

Two of these compounds, glibenclamide and glipizide, are available on the Fiji Essential Drugs List.

They act on the pancreatic beta-cells and induce insulin secretion.

Glibenclamide is predominantly cleared by the kidneys and it is recommended in younger patients. In contrast, glipizide is cleared by the liver and the kidneys and it is the recommended drug in older patients and in patients with renal impairment.

Sulphonylureas are used in lean type 2 diabetics. They can be combined with metformin if the diabetes control is inadequate.

These drugs are not recommended in pregnancy and lactating mothers.

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<sup>1</sup> For simplification, the term "diabetes" is used throughout the text of the guidelines and refers to the disease called "diabetes mellitus."

Hypoglycaemia is the major adverse effect especially when there is significant renal impairment. This is less likely with shorter-acting drugs (i.e. glipizide) but much more likely with longer-acting compounds (i.e. glibenclamide).

Glipizide can be given as a single dose up to 15 mg/day orally before meals and in two divided doses above 15 mg up to a maximum of 30 mg/day.

The 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.

### c. Insulins

There are three insulin preparations available in the Fiji EDL. In this section, the pharmacokinetics of these preparations is discussed. The usage of these preparations is discussed under **Section 4**.

Insulin is given using conventional disposable insulin syringes. Insulin pens and pre-filled syringes are expensive options and are available only in the private sector.

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.**

	<b>Effect onset (h)</b>	<b>Maximum effect (h)</b>	<b>Duration (h)</b>
Short-acting soluble insulin, 100 u/ml (Actrapid HM, Humulin R )	0.5	2-5	6-8
Intermediate-acting isophane insulin, 100 u/ml (Protaphane HM, Humulin NPH)	1-2.5	4-12	16-24
Biphasic isophane insulin, 100 u/mL (Mixtard 30/70, Humulin 30/70)	0.5-1	2-12	16-24

<sup>a</sup>Currently not available in the Fiji EDL.

## 1.2 Drugs for treating complications and coexisting conditions

### 1.2.1 Fludrocortisone

This fluorinated, orally active steroid can be used to treat postural hypotension in patients with diabetic autonomic neuropathy.

It acts on the distal tubule of the nephron to enhance the reabsorption of sodium and water and thereby expand the plasma volume. Plasma volume is not abnormally low in autonomic neuropathy but the control of peripheral vasoconstrictor tone is lost and a higher than average plasma volume can counteract the fall in blood pressure on standing.

The major adverse effect is excessive salt and water retention manifesting as dependent oedema or, rarely, pulmonary oedema.

It is available as a 100 microgram-tablet and the dose varies from 50 to 300 microgram ( $\mu\text{g}$ ) daily.

### **1.2.2 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 the doses advocated for the relief of pain in diabetic neuropathy, the major adverse drug effects are usually dry mouth and occasionally blurring of vision.

The usual dose is 50 to 75 mg at night.

### **1.2.3 Carbamazepine**

Like amitriptyline, carbamazepine has been demonstrated to have a place in the treatment of several pain syndromes – notably trigeminal neuralgia. The mode of action of this anticonvulsant in the treatment of pain from diabetic neuropathy is unknown but there is good evidence 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 cerebellar manifestations such as slurred speech or mild ataxia should be looked for and plasma concentrations of carbamazepine should be measured if toxicity is suspected.

### **1.2.4 Glucagon<sup>2</sup>**

Glucagon is the naturally occurring hyperglycaemic hormone secreted by the pancreas. It has a role in reversing hypoglycaemia in a patient on insulin or taking sulphonylureas. Although not routinely available in Fiji, it would have a role in the out-of-hospital reversal of hypoglycaemia when the patient is unable to take fluids or to swallow food.

Unconscious patients would be expected to resume consciousness within 6 minutes after glucagon injection.

Glucagon can be obtained as a ready-for-injection kit which patients can carry with them for the use of family members or others providing emergency treatment in the community.

### **1.2.5 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 Fiji EDL. The reader is advised to refer to **Section 2.5** for the usage of enalapril.

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<sup>2</sup> Glucagon is not available in the Fiji EDL.

## 2 Classification, diagnosis and general management of diabetes

### 2.1 Types of diabetes

The important types of diabetes mellitus in clinical practice are discussed below.

#### 2.1.1 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, and therefore, 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.

#### 2.1.2 Type 2 diabetes

Previously known as non-insulin dependent diabetes mellitus (NIDDM), type 2 diabetes is the commonest type seen in Fiji and worldwide. The onset is 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.

Abnormalities in pancreatic insulin secretion, abnormal regulation of hepatic glucose 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/m<sup>2</sup>, 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.

#### 2.1.3 Secondary diabetes

Secondary diabetes occurs in the following situations:

- endocrine disorders - acromegaly, Cushing's disease, thyrotoxicosis and sometimes in phaeochromocytoma;
- during treatment with corticosteroids;
- thiazide diuretic therapy (it may impair glucose tolerance);
- pancreatic destruction due to surgery, cancer and chronic diseases of the pancreas.

### 2.2 Screening for diabetes

The Fiji World Health Organization (WHO) Steps Survey of Risk Factors for Non-Communicable Diseases conducted in 2002 have shown that 12% of Fiji's population suffers from diabetes. Hence, 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:

### 2.2.1 Patients at risk

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

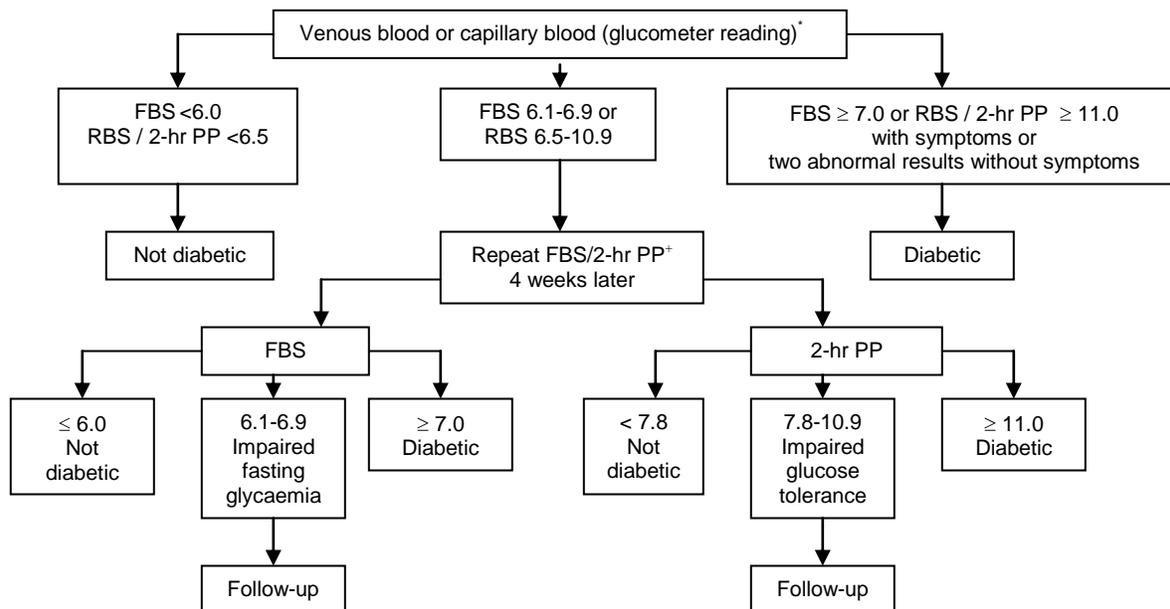
### 2.2.2 Patients with typical symptoms of diabetes

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

### 2.2.3 Patients suffering from conditions suggestive of diabetes

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

## 2.3 Diagnosis of diabetes mellitus



\* All blood sugar levels are in mmol/L. FBS – fasting blood sugar; RBS – random blood sugar. \* PP – post-prandial or after meal. Note that hemoglobin A<sub>1c</sub> (Hb A<sub>1c</sub>) estimation is not recommended in the initial diagnosis of diabetes. It is useful only for monitoring the control of diabetes. The values above do not apply to pregnant mothers. Please refer to **Section 8** for details.

**Figure 1. Diagnosis of diabetes mellitus based on blood sugar levels.**

## 2.4 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 post-prandial blood sugars. **About 30% of pre-diabetic patients develop overt diabetes in five years.**

## 2.5 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
- 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.

### 2.5.1 Adequate blood sugar control

Blood sugar control is affected by four factors:

- food intake,
- physical activity,
- stress, and
- drug treatment.

#### a. Food intake

Refer all newly diagnosed diabetics to a dietician whenever possible.

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.

More detailed recommendations are beyond the scope of these guidelines and need to be obtained in consultation with a dietitian. A diabetic's diet does not have to be dull and unvaried. 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<sup>3</sup> 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/m<sup>2</sup>). This will also assist in the control of hyperlipidemia and blood pressure.

#### **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 moderate-intensity physical activity every day. This includes activities such as brisk walking, cycling, and gardening. Additional health benefits can be obtained by more vigorous activities (such as dancing, jogging, swimming continuous laps, or heavy digging in the garden) or through longer durations of moderate-intensity activities.

#### **d. Drug therapy**

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

### **2.5.2 Risk factor modification**

#### **a. Smoking**

Diabetics should not smoke.

#### **b. Hypertension** (also refer to *Cardiovascular Drug Guidelines*)

This is 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), slow release calcium channel blockers (e.g. nifedipine), and loop diuretics (e.g. furosemide) can also be used. In Fiji, methyldopa is available and can be used if the above drugs are not available. A combination of the above drugs might be 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.

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<sup>3</sup> 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).

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

- i. 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.
- ii. In the presence of renal impairment and/or significant proteinuria (>1 g/day or ++++ 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.

### **c. Hyperlipidemia**

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 drugs are either statins (e.g. lovastatin, simvastatin, pravastatin, atorvastatin) or fibrates (e.g. gemfibrozil). These drugs are not available in the EDL at present.

The reader is advised to refer to the booklet on *Cardiovascular Guidelines*.

### 3 Targets of diabetes control

As part of the diabetes management program, it is important to have a set of targets for diabetes control. These targets should be discussed between the patient and the doctor before initiating treatment and during each follow-up visits.

**Table 2. Targets of diabetes control.**

Indicator	Very good control	Fair control	Could be better
Fasting Blood glucose (mmol/L)	4.0 - 6.0	6.1-7.0	≥ 7.1
2-hour post-prandial (mmol/L)	4.0 – 8.0	8.1-10.0	≥10.1
HbA 1c (%)	< 6.0	6.0 – 7.0	≥ 7.0
Total cholesterol (mmol/L)	< 4.0	4.1 – 4.9	≥ 5.0
HDL-cholesterol (mmol/L)	> 1.0	≤1.0 – 0.9	< 0.9
LDL-cholesterol (mmol/L)	< 3.0	3.0 – 4.0	> 4.0
Triglycerides (mmol/L)	< 1.5	1.6 – 2.0	> 2.0
Blood pressure (mm Hg)	<130/80	>130/80 - <140/90	≥ 140/90
Body mass index (kg/m <sup>2</sup> **) Ideal BMI: 20 – 25 m <sup>2</sup>	M: < 25 F: < 24	M: < 27 F: < 26	M ≥ 27 F ≥ 26

\* HbA1c – amount of circulating glycosylated haemoglobin, a measure of the overall control over preceding 3 months.

\*\* BMI ranges recommended for Pacific Islanders are somewhat higher at 20.5-27.0.

Source: Schultz, D. 1999. *BMI Cut-off for Pacific Islanders*. National Food and Nutrition Centre, Suva.

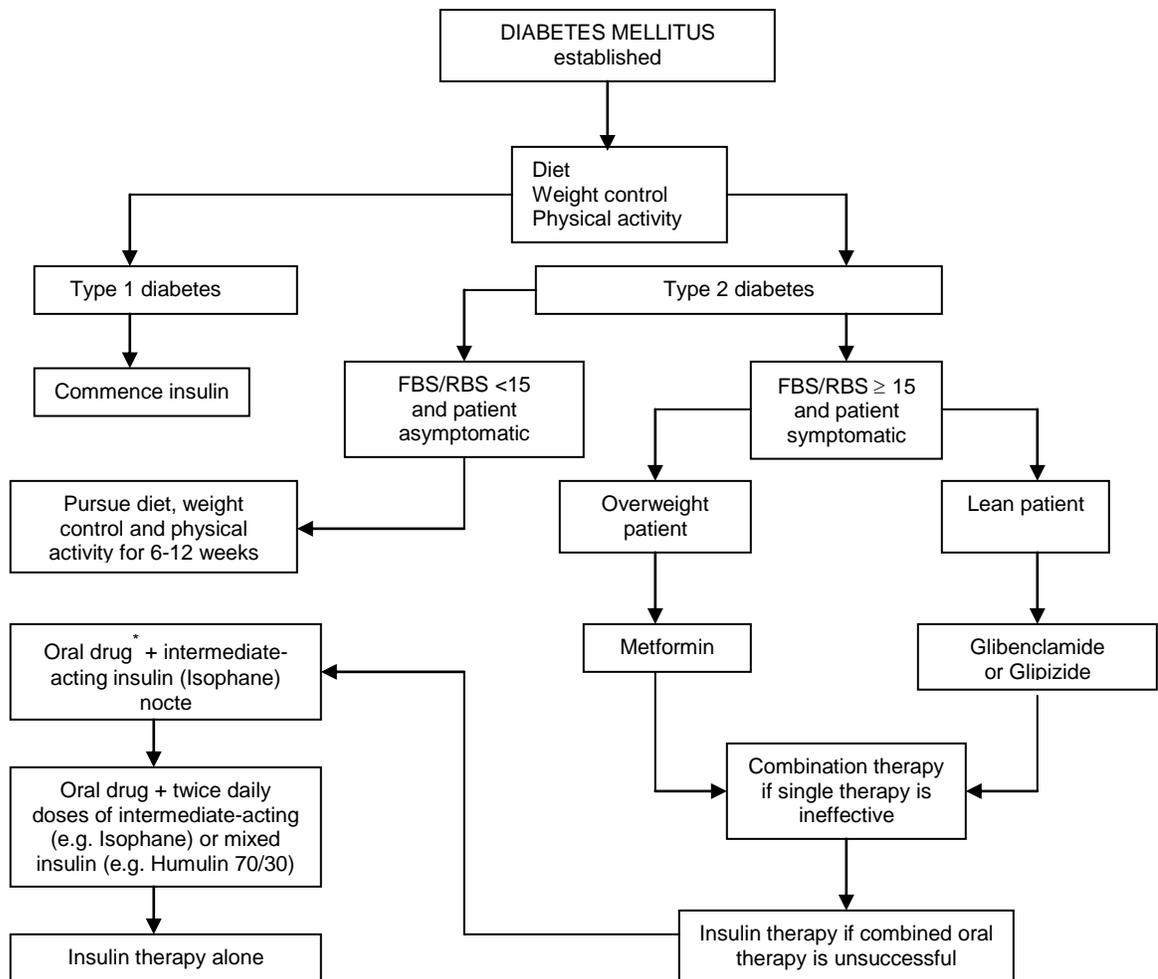
# 4 Specific aspects in the management of diabetes

## 4.1 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. These regimens can produce good glucose control in type 2 diabetes; and if it does, then these should be pursued. Drug therapy should only be considered if blood sugar levels remain uncontrolled after 6-12 weeks.

The discussion below refers to those patients whose blood sugar levels are not adequately controlled with non-pharmacological therapy. The reader is advised to refer to Section 1 for details of the drugs mentioned in this section.



\* Metformin is preferable over sulfonylureas.

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

## 4.2 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.

## 4.3 Type 2 diabetes

### 4.3.1 Obese patients (BMI > 30 kg/m<sup>2</sup>)

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 or glipizide (see below).

### 4.3.2 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 daily with meals or after meals. This drug is preferred in younger patients.*

OR

*Glipizide 2.5 to 15 mg single dose or twice daily up to 30 mg daily taken with meals or before meals. This drug is preferred in older patients and those patients with renal, hepatic and cardiac dysfunction.*

### 4.3.3 Combination oral treatment

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

*Metformin + glibenclamide or glipizide (doses as above).*

### 4.3.4 Insulin treatment in type 2 diabetes

#### a. Deciding when to start

The indications when to start insulin in type 2 diabetes are the following:

- 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.*

**c. Insulin regimens<sup>4</sup>**

**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 the blood sugar levels.

**ii. Twice daily regimen**

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-third in the evening. However, insulin doses should be adjusted based on the blood sugar levels and increments of 5 units per dose are recommended.

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<sup>4</sup> For both insulin regimens, extra soluble insulin 5 units subcutaneously can be given if blood sugars are not controlled.



# 5 Special situations in the management of diabetes

## 5.1 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.

## 5.2 Fasting

Many diabetics need to fast for religious or other reasons.

### 5.2.1 Type 1 diabetes

For type 1 diabetics, their usual daily insulin dose can be divided into two doses given before each of the two main meals of the day.

### 5.2.2 Type 2 diabetes

The timing of the dose of the oral hypoglycaemic is important.

For those patients on metformin, doses can be rearranged to coincide with the two main meals of the day.

For those patients on sulfonylureas: for once daily dosage, give medication before the first main meal and for those on twice daily dosage, give the medication before the two main meals.

## 5.3 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.

## **5.4 Traveling**

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.

## **5.5 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.

### **5.5.1 Local anaesthesia**

#### **a. Patients with normal blood sugar levels**

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.

### **5.5.2 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  $\geq 12$  mmol/L.

**ii. Patients on insulin therapy**

It is recommended that patients be admitted a day before surgery and be started on multiple-dose (“QID”) insulin regimen. Give extra soluble insulin 5-10 units subcutaneously if the blood sugar level is  $\geq 12$  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-insulin-potassium (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.**

# 6 Management of acute complications of diabetes

## 6.1 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:

*Give dextrose 50% 50 ml intravenously followed by continuous 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.

## 6.2 Diabetic ketoacidosis

### 6.2.1 General considerations

**Diabetic ketoacidosis (DKA)** occurs commonly in Type 1 diabetics. The diagnostic features include:

- vomiting,
- abdominal pain,
- Kussmaul's breathing,
- dehydration,
- ketotic breath,
- mental confusion progressing to coma.

It is necessary to test urine for moderate to large ketone bodies. Arterial blood gas is desirable if facilities are available.

**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.

## **6.2.2 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  $\leq 12$  mmol/L, change intravenous fluid to either dextrose saline or dextrose 5%.

### **b. Insulin**

*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 venous access cannot be established, give:

*Short-acting insulin intramuscularly 8 units /hour.*

Blood sugar should be measured every hour and insulin doses adjusted<sup>5</sup>. Insulin doses can be halved when blood glucose reaches  $\leq 12$  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.

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<sup>5</sup> For adjustment of doses of insulin infusion, refer to the appendix.

### c. **Electrolytes**

#### i. **Potassium**

Insulin takes glucose and potassium into the cells and their respective serum concentrations fall. A safe and cautious approach is to initiate supplementary intravenous potassium at a rate of no more than 10-20 mmol/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.

### d. **Other measures**

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.

## 6.2.3 **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 return.

**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 to guide the rate of fluid replacement according to body weight and degree of dehydration are available at pediatric units of respective divisional hospitals.

## 6.3 **Hyperosmolar, hyperglycaemic state**

This is a relatively uncommon event usually occurring as a dramatic presenting feature or as a complication of type 2 diabetes.

It presents with a history of thirst, polyuria and progressive impairment of consciousness commonly in a patient who is 60 years or older. It differs from DKA in that patients with hyperosmolar, hyperglycaemic state do not develop ketoacidosis.

Investigations reveal very high blood glucose, usually higher than 30 mmol/L, the serum sodium is often elevated and the calculated serum osmolality  $>320$  mOsm/l.<sup>6</sup>

### **Management**

The treatment is similar to that in DKA (see above).

Intravenous isotonic saline, low dose intravenous insulin (4-6 u/hour by infusion) and careful attention to serum potassium concentrations are the central strategies. Careful monitoring is required as in DKA.

On recovery, the patient may not need long-term insulin therapy. After an initial period of stabilisation with insulin, most patients with type 2 diabetes who present in a hyperosmolar, hyperglycaemic state can be controlled with oral hypoglycaemic drugs combined with diet.

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<sup>6</sup> Serum osmolality =  $2(\text{Na} + \text{K}) + \text{urea (mmol/L)} + \text{blood sugar (mmol/L)}$ .

# 7 Management of late complications of diabetes

## 7.1 Retinopathy

Diabetic retinopathy is a major cause of blindness in Fiji. 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. Patients should be referred to an ophthalmologist if:

- they have had diabetes for longer than 5 years.
- if there is any visual impairment (vision worse than 6/12).
- if there are any exudates or haemorrhages on fundoscopy.

**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.

## 7.2 Neuropathy

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

### 7.2.1 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.*

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.

### 7.2.2 Autonomic neuropathy

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 µg orally daily.*

### 7.3 Foot infections

Diabetic foot infection might involve the skin and soft tissue as well as underlying muscle and bone and should always be regarded as serious. Distal neuropathy with or without vascular damage puts feet at risk from ulceration and infection which may lead to gangrene and the need for amputation.

Treat infection early and aggressively with proper antibiotics. Diabetic infections are often caused by a mixture of organisms (aerobes and anaerobes).

*For mild to moderate infections, give metronidazole 400 mg orally 8-hourly PLUS flucloxacillin 500 mg orally 6-hourly. For severe infections, refer to divisional hospitals.<sup>7</sup>*

Control blood sugar to prevent rapid spread of infection.

Advice on proper foot care and wound management. Consider early wound debridement and use of normal saline instead of strong dressing solutions.

All diabetics should have a foot assessment once a year.

**Foot care education should be emphasized to all patients on every visit.**

### 7.4 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. In Fiji, the recommended drug is:

*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.

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<sup>7</sup> Refer to *Antibiotic Guidelines 2005* for treatment of severe infections.

For details of control of blood pressure and hyperlipidaemia, refer to **Section 2**.

For advanced chronic renal failure, renal replacement therapy in the form of dialysis or renal transplant needs to be considered. Refer to consultant physician for advice.

**Good blood pressure control as well as good glucose control is essential in all diabetics to reduce progression of complications.**

## 8 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.

### 8.1 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.

### 8.2 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.

#### 8.2.1 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 regimen, diabetes may be controlled with:

*Mixed insulin twice daily; dose determined by blood glucose measurement (Refer to section 4.3).*

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.

#### 8.2.2 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.

#### 8.2.3 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.

### 8.3 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.

#### 8.3.1 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  $\geq 8$  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  $\geq 8$  mmol/L, the result is suggestive of gestational diabetes but further formal testing with a fasting oral glucose challenge should be done for confirmation. However, blood sugar of  $\geq 10$  mmol/L at one hour is diagnostic of gestational diabetes.

#### 8.3.2 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.*

## 8.4 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.

## 8.5 After delivery

Women with gestational diabetes **should be followed up** with an oral glucose tolerance test about 6 week's post-partum. 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.

## Appendix

### INSULIN INFUSION

#### Preparation

##### 1. Infusion by electronic pump

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

*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 (CBG) (mmol/L)	Infusion pump (ml/hr)		Intravenous drip (Preparation 2)	
	Preparation (1)	Preparation (2)	Macrodrops/min	Microdrops/min
	<6.0	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.

