These guidelines have been withdrawn

MOH clinical practice guidelines are considered withdrawn five years after publication unless otherwise specified in individual guidelines. Users should keep in mind that evidence-based guidelines are only as current as the evidence that supports them and new evidence can supersede recommendations made in the guidelines.

CLINICAL PRACTICE GUIDELINES

Diabetes Mellitus

Ministry of Health

Jun 2006

MOH Clinical Practice Guidelines 3/2006

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial, as part of the body of literature of overall good quality and consistency, addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies, but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Diabetes Mellitus

MOH Clinical Practice Guidelines 3/2006

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

It is no exaggeration to describe diabetes as one of the major contributors to ill health and premature mortality worldwide. Globally, it is estimated that at least 1 in 20 deaths are attributable to diabetes across all ages, and, in adults aged 35 to 64, the proportion is at least 1 in 10 deaths. If the current trend continues, it is estimated that by 2030, the number of people with diabetes will more than double. In Singapore, the prevalence of diabetes is 8.2% as determined in the 2004 National Health Survey (NHS) and it is the eighth commonest cause of death.

Guidelines for the *Management of Diabetes Mellitus* in Singapore were first drawn up by the National Diabetes Commission in 1993. In 1999 the MOH Clinical Practice Guidelines on Diabetes Mellitus were published. For guidelines to be most useful, they need to incorporate the latest evidence from the scientific literature, and it is timely to issue a new edition of these guidelines. Important changes in this new edition include an update on diagnosis and screening for diabetes and glucose intolerance, and recent clinical trial evidence on new classes of antidiabetic drugs.

I hope that all medical practitioners will find this set of guidelines useful in their management of patients with diabetes mellitus.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Contents

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Diagnosis and Screening of Diabetes Mellitus in Singapore

B In subjects with unequivocal hyperglycaemia with acute metabolic decompensation diabetes mellitus can be diagnosed without further testing (pg 20).

Grade B, Level III

B In patients with typical symptoms, diabetes mellitus can be diagnosed if any one of the following is present:

1. Casual plasma glucose ≥11.1 mmol/l
2. Fasting plasma glucose ≥7.0 mmol/l
3. 2-hour post-challenge glucose ≥11.1 mmol/l

Other individuals should have a repeat test on a subsequent day (pg 20).

Grade B, Level III

B Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus (pg 20).

Grade B, Level III

B We should recognise intermediate states of glucose metabolism termed impaired fasting glycaemia and impaired glucose tolerance in accordance with the report of the WHO consultation (pg 21).

Grade B, Level III

B All subjects with fasting plasma glucose from 6.1 to 6.9 mmol/l should undergo a 75 g oral glucose tolerance test to determine if they have impaired glucose tolerance or diabetes mellitus (pg 21).

Grade B, Level III

C Screening of asymptomatic individuals for diabetes mellitus should be carried out in accordance with the Ministry of Health Clinical Practice Guidelines for Health Screening (6/2003).

Grade C, Level IV

N.B. The workgroup recommends lowering the cut-off value of triglycerides at which the individual is considered at increased risk of diabetes from 2.82 in MOH clinical practice guidelines on health screening to 2.3 mmol/l. (pg 22).

Lifestyle Modification

B Lifestyle modification is a cornerstone of diabetes management. Medical nutrition therapy and exercise prescription should be the initial therapy in obese (BMI ≥ 30) and overweight (BMI ≥ 25) type 2 diabetic patients unless they are symptomatic or severely hyperglycaemic (pg 31).

Grade B, Level IIa

C Medical nutrition therapy should be individualized. Saturated fat intake should not exceed 10%, with carbohydrates making up 50-60% and proteins 15-20% of total calorie intake. Diet should include foods from each of the basic food groups (pg 31).

Grade C, Level IV

C An exercise programme tailored to suit the individual's age, fitness, aptitude and interest should be prescribed (pg 32).

Grade C, Level IV

C A pre-exercise evaluation to identify macrovascular, microvascular and neurological complications is recommended (pg 32).

Grade C, Level IV

C Individuals with diabetes, especially those on insulin treatment, should receive specific education on the prevention of exercise-induced hypoglycaemia (pg 32).

Grade C, Level IV

C Individuals with diabetic neuropathy should avoid exercises associated with repetitive foot trauma (pg 33).

Grade C, Level IV

C Individuals with severe diabetic proliferative retinopathy should avoid activities that dramatically elevate blood pressure (pg 33).

Grade C, Level IV

B Individuals with diabetes should be discouraged from smoking (pg 33).

Grade B, Level III

B Diabetic patients with poor glycaemic control or dyslipidaemia should be discouraged from consuming alcohol (pg 33).

Grade B, Level IIb

Pharmacotherapy in Diabetes Mellitus

A Type 2 diabetic patients may initially be treated with lifestyle modification (diet and exercise) for 2 to 4 months unless they are symptomatic or severely hyperglycaemic (i.e. random blood glucose >15 mmol/l or fasting blood glucose >10 mmol/l). Oral antihyperglycaemic agents should be started, if glycaemic targets are not achieved. Insulin therapy should be started, if optimal combination therapy fails to attain target control (i.e. 2 consecutive HbA_{1c} values failed to reach ≤8% over 3-6 months interval) (pg 36).

Grade A, Level Ia

A Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes. Stepwise therapy with multiple pharmacological therapies is often needed over time to maintain target glucose control. Two or more oral agents, or insulin therapy, either alone or in combination with oral agents, may be required (pg 35).

Grade A, Level Ia

A All type 1 diabetic patients must receive insulin. Multiple daily injections (3 or more) or the use of continuous subcutaneous insulin infusion (CSII or insulin pump therapy) may be required to achieve target glucose levels (pg 44).

Grade A, Level Ib

Glycaemic Control: Assessment and Targets

GPP Health care professionals should be familiar with the practical use of glucometers (pg 48).

GPP

B Self-monitoring of blood glucose (SMBG) should be initiated in most patients with diabetes, especially in insulin-treated subjects, in pregnant women with pre-existing diabetes or gestational diabetes, and in patients who are at increased risk of developing hypoglycaemia (pg 48).

Grade B, Level IIa

GPP The visual method of self-monitoring of blood glucose is not recommended (pg 49).

GPP

A Besides receiving proper training in the use of blood glucometers, patients must be educated on the interpretation of the results and, where possible, taught to modify treatment according to blood glucose levels (pg 50).

Grade A, Level Ib

C Testing for glucose in urine is not recommended for monitoring of glycaemic status (pg 50).

Grade C, Level IV

C Testing for ketones in the urine is recommended in patients with Type 1 diabetes, pregnant women with pre-existing and gestational diabetes, if there is:

- Acute illness or stress
- Persistent elevation of blood glucose (>16.7 mmol/l)
- Any symptom suggestive of ketoacidosis (nausea, vomiting, abdominal pain or acetone breath) (pg 51).

Grade C, Level IV

GPP Routine monitoring of blood ketones is not recommended for type 1 or type 2 diabetic patients (pg 51).

GPP

C Glycated haemoglobin (HbA_{1c}) testing should be performed routinely in all patients with diabetes. The frequency of testing for any individual patient may vary according to the treatment regimen used and the status of glycaemic control (page 52).

Grade C, Level IV

C The following schedule is recommended for glycated haemoglobin testing:

- 3- to 4-monthly in patients with unstable glycaemic control, failure to meet treatment goals, recent adjustment in therapy, or intensive insulin therapy.
- 6-monthly in patients who have stable glycaemic control and who are meeting treatment goals (pg 52).

Grade C, Level IV

C The targets of glycaemic control should be defined for each patient, with patient participation in the process (pg 53).

Grade C, Level IV

A "Optimal" glucose control should be the target for the majority of patients with diabetes. This refers to glucose levels that approach the normal range (HbA_{1c} 6.5-7.0%; preprandial glucose 6.1-8.0 mmol/l) and is associated with a low risk of developing microvascular complications (pg 53).

Grade A, Level Ib

A "Suboptimal" glucose control (HbA_{1c} 7.1-8.0%; preprandial glucose 8.1-10.0 mmol/l) may be the target in special subsets of patients who are vulnerable to injury from the increased risk of severe hypoglycaemia associated with "optimal" glucose control (pg 53).

Grade A, Level Ib

Prevention of Cardiovascular Disease in Diabetes Mellitus

GPP The assessment of cardiovascular risk in persons with type 2 diabetes mellitus should include:

1. A medical history, which should include:
   a. A smoking history.
   b. A history of hypertension and/or medication taken for the treatment of hypertension.
   c. A history of pre-existing cardiovascular disease (CVD) to include angina pectoris, myocardial infarction, stroke, or peripheral vascular disease.
2. A physical examination which should include an assessment of peripheral pulses.

3. Blood pressure should be measured each time a patient with type 2 diabetes mellitus is seen in the clinic.
4. Fasting serum lipids should be measured at the time of diagnosis and at least once a year if they are in the optimal range.
5. Assessment of urine for microalbuminuria or proteinuria should be carried out at the time of diagnosis and at least once a year in all patients.
6. In view of the fact that persons with type 2 diabetes mellitus are more likely to experience atypical symptoms of coronary heart disease (CHD), a routine resting ECG is recommended at baseline. Subsequent ECG may be performed when clinically indicated. Specific abnormalities which may suggest CHD should be assessed by a cardiologist for appropriate risk stratification (pg 57).

GPP

B The primary prevention of CVD should form one of the major goals of therapy in the management of type 2 diabetes mellitus (pg 57).

Grade B, Level III

B Type 2 diabetes mellitus should be considered a CHD risk equivalent (pg 57).

Grade B, Level III

C An assessment of the CVD risk factors present is recommended for all persons with type 2 diabetes mellitus in order that appropriate therapy be instituted (pg 57).

Grade C, Level IV

A The prevention of CVD in persons with type 2 diabetes mellitus must take a global approach with intervention targeting all aspects of the disease (pg 58).

Grade A, Level Ib

C Therapeutic lifestyle modification (through modulation of diet and physical activity) should form the mainstay of strategies to reduce cardiovascular risk associated with type 2 diabetes mellitus (pg 58).

Grade C, Level IV

B All possible efforts should be taken to encourage persons with type 2 diabetes mellitus to stop smoking (pg 59).

Grade B, Level III

Hypertension in patients with diabetes mellitus

A The target of hypertension treatment in type 2 diabetes mellitus should be < 130/80 mmHg (pg 59).

Grade A, Level Ib

A Lifestyle modification and drug therapy should be instituted for all subjects with blood pressure >130/80 mmHg (pg 59).

Grade A, Level Ib

A The choice of first line therapy can include (a) diuretics (D) (b) β-blockers (BB) (c) ACE inhibitors (ACEI) (d) calcium channel blockers (CCB) (e) angiotensin II receptor blockers (ARB) and should be based on the cost of the drug and any compelling indications and contraindications for its use (pg 60).

Grade A, Level Ib

Dyslipidaemia in patients with diabetes mellitus

A For the prevention of CHD, the first priority is optimization of the LDL cholesterol. This is followed by HDL-cholesterol and then triglyceride (pg 63).

Grade A, Level Ia

C The exception is in individuals with levels of TG >4.5 mmol/l (400 mg/dl) who have an increased risk of acute pancreatitis. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis (pg 63).

Grade C, Level IV

C Fibrate therapy should be considered as first line therapy for those with TG > 4.5 mmol/l (400 mg/dl) to prevent acute pancreatitis (pg 63).

Grade C, Level IV

A For all other patients with type 2 diabetes mellitus and LDL cholesterol >2.6 mmol/l (100 mg/dl), the treatment of choice is an HMG CoA reductase inhibitor (statin) (pg 63).

Grade A, Level Ia

A For patients with LDL cholesterol <2.6 mmol/l (100 mg/dl) and low HDL-cholesterol (<40 mg/dl), a fibrate can be started as the initial lipid lowering therapy (pg 63).

Grade A, Level Ib

C If HDL cholesterol remains low (<1 mmol/l or 40 mg/dl) after achieving the LDL goal with a statin, combination therapy can be considered in selected high risk patients, such as those with type 2 diabetes mellitus and existing CHD (pg 63).

Grade C, Level IV

B When combining a statin with a fibrate, gemfibrozil should not be used (pg 64).

Grade B, Level III

Anti-thrombotic agents in patients with diabetes mellitus

A All patients with type 2 diabetes mellitus over the age of 45 years or who have concomitant hypertension, dyslipidaemia or pre-existing CVD (CHD, stroke or peripheral arterial disease) should be treated with aspirin 75-100 mg per day. In the presence of contraindications for aspirin therapy, other antiplatelet agents such as clopidogrel may be a reasonable alternative for patients with high risk (pg 64).

Grade A, Level Ia

Prevention and Treatment of Diabetic Nephropathy

C Screening for albuminuria should begin at 5 years after the diagnosis of type 1 diabetes; it should, however, begin immediately with the diagnosis of type 2 diabetes. Thereafter, screening for albuminuria should be done annually (pg 70).

Grade C, Level IV

GPP Serum creatinine should be measured at least annually (pg 70).

GPP

C The blood pressure target in all diabetic persons should be less than 130/80 mmHg. Diabetic patients with proteinuria levels exceeding 1 gram should try to have their BP lowered to less than 125/75 mmHg (pg 72).

Grade C, Level IV

A In the absence of microalbuminuria or overt nephropathy, the principal intent is that of reducing the risk of a cardiovascular event. There is evidence for the initial antihypertensive agent to be from one of these classes: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers, diuretics, calcium channel blockers (pg 73).

Grade A, Level Ib

A In the presence of microalbuminura, both ACE inhibitors and ARBs can be used (pg 73).

Grade A, Level Ib

A In the presence of overt nephropathy in type 1 diabetes, there is evidence that an ACE inhibitor can retard the progression of otherwise progressive renal disease (pg 74).

Grade A, Level Ib

A In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease (pg 74).

Grade A, Level Ib

GPP The serum creatinine and potassium should be checked within 4 weeks of initiation of treatment to detect any rise in the serum creatinine or hyperkalaemia (pg 74).

GPP

GPP Progressive but non-continuous rise in the serum creatinine may be seen over 2 to 3 months after starting on ACE inhibitor or ARB. A short-term rise of less than 30% in the serum creatinine should not necessitate withdrawing the ACE inhibitor or ARB. Nevertheless, the possibility that there may be critical renal artery stenosis should be considered, especially in the presence of a renal artery bruit or refractory hypertension or asymmetric kidney sizes on ultrasound (pg 74).

GPP

GPP Therapy should aim to reduce albuminuria as much as possible, and it is reasonable to aim for a proteinuria target of less than 1 g/day or at least 50% of the pre treatment value (pg 75).

GPP

GPP Type 1 diabetic patients with overt nephropathy should be maintained on a low protein diet of 0.8 g/kg/day (pg 75).

GPP

GPP A nephrology referral is recommended when there are unexpected or rapid decline in renal function, difficulties with hyperkalaemia, atypical features e.g. haematuria, presence of casts in the urine sediment, presence of a renal bruit, difficult BP control, nephrotic range proteinuria (>3 g/day), and absence of retinopathy (pg 75).

GPP

Prevention and Management of Eye Complications

Screening

C All patients diagnosed with diabetes require regular visual acuity assessment and eye examinations by trained personnel to screen for diabetic retinopathy using a test of adequate sensitivity (pg 78).

Grade C, Level IV

C Type 1 diabetic patients should be examined 3-5 years after diagnosis of diabetes, and at least once yearly subsequently. Type 2 diabetic patients should have an ocular assessment at the time of diagnosis and at least once yearly subsequently (pg 79).

Grade C, Level IV

C Retinal screening preferably using retinal photography, or direct ophthalmoscopy (if retinal photography is not available) through dilated pupils is recommended (pg 78).

Grade C, Level IV

Management of systemic risk factors

A Good glycaemic control (HbA_{1c} preferably 6.5 to 7.5%) should be instituted to reduce the risk of retinopathy (pg 80).

Grade A, Level Ib

A Good control of blood pressure at or below 130/80 mmHg should be instituted to reduce the progression of diabetic retinopathy (pg 81).

Grade A, Level Ib

C Significant hyperlipidaemia should be treated to retard diabetic retinopathy (pg 81).

Grade C, Level IV

Referrals

GPP Diabetic patients found to have diabetic retinopathy by their physicians should be referred for further ophthalmological assessment (pg 84).

GPP

A Timely laser therapy should be offered to patients with proliferative diabetic retinopathy and diabetic macular oedema. Panretinal and focal/grid laser treatment results in at least a 50% reduction in the risk of visual loss (pg 85).

Grade A, Level Ib

Treatment

A Laser photocoagulation should be instituted for severe and proliferative retinopathy as it produces a 50% reduction in risk for severe visual loss and need for vitrectomy (pg 85).

Grade A, Level Ib

Prevention of Diabetic Foot Complications

B All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions (pg 92).

Grade B, Level IIb

B The assessment of the feet involves risk identification, treatment and patient education appropriate to the level of risk (pg 92).

Grade B, Level IIa

A All patients, regardless of risk category, should receive ongoing education on footcare and footwear advice (pg 93).

Grade A, Level Ib

B Patients identified with foot-related risk conditions should have access to a specialized footcare team which should include diabetes specialist, podiatrist, physiotherapist trained in diabetes, diabetes nurse educator and vascular and orthopaedic surgeon (pg 93).

Grade B, Level III

A Urgent referral to a specialized footcare team is needed in the presence of ulcerations, severe foot infection and gangrene (pg 91).

Grade A, Level Ib

Management of Women with Pregestational and Gestational Diabetes Mellitus

Preconception care

B All diabetic women in the reproductive age group should receive pre-pregnancy counselling, particularly before starting a family (pg 98).

Grade B, Level IIa

Screening and diagnosis

B Women at high-risk for gestational diabetes (GDM) should undergo an OGTT as early in pregnancy as feasible. Re-evaluation may be necessary at 28 weeks if glucose intolerance is not present at the early screen (pg 99).

Grade B, Level IIa

B In all other patients, urine for glucose should be obtained at each antenatal visit and random blood sugar levels ascertained when there is ≥1+ glycosuria. A diagnostic test is necessary if the random plasma blood glucose >6.6 mmol/l more than 2 hours after a meal, or >7.0 mmol/l within 2 hours of a meal (pg 99).

Grade B, Level III

Antenatal care

B In gestational diabetes (GDM), dietary control should be used in the first instance to attain glycaemic goals. If nutritional therapy does not consistently maintain a fasting or pre-meal capillary blood glucose of <5.5 mmol/l and/or a 2-hour postprandial capillary blood glucose of <6.7 mmol/l on two or more occasions within a 1-2 week interval, insulin therapy should be considered (pg 100).

Grade B, Level IIa

B In established diabetics (pregestational diabetes), intensive insulin treatment is often necessary to maintain target blood glucose levels (pg 100).

Grade B, Level IIb

B Maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting or premeal state, and/or <7.8 mmol/l 1 hour after meals, and/or <6.7 mmol/l 2 hours after meals (pg 100).

Grade B, Level III

B All women diagnosed with GDM and pregestational DM should receive specialized care (pg 100).

Grade B, Level III

Infants of diabetic mothers

B Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life. Infants of diabetic mothers should be fed early (pg 103).

Grade B, Level III

Postnatal management

B Breastfeeding is not contraindicated in women with diabetes (pg 103).

Grade B, Level III

B An OGTT should be performed at least 6 weeks postpartum and the patient reclassified and counselled according to criteria accepted in the non-pregnant state (pg 103).

Grade B, Level IIb

Contraception

B Low dose oestrogen-progestin oral contraceptives and the intra-uterine contraceptive devices are not contraindicated in women with previous GDM (pg 104).

Grade B, Level III

B Oestrogen-progestogen contraceptives should be avoided in women with complications of diabetes and those at risk of vascular disease (pg 104).

Grade B, Level III

Management of the Child and Adolescent with Diabetes Mellitus

B In childhood type 1 diabetes mellitus, the aims of treatment are:

a. Normal physical growth and pubertal development.
b. Normal psychosocial development and full participation in age-appropriate activities.
c. Good glycaemic control with minimal hypoglycaemia.
d. Absence of diabetic ketoacidosis.
e. Minimization and early detection and treatment of complications. (pg 107)

Grade B, Level IIa

B The care of diabetes in childhood and adolescence, whether type 1 or type 2, is best accomplished by a multi-disciplinary team in an institutional setting (pg 107).

Grade B, Level IIa

B Screening for diabetes should be considered for children and adolescents who are overweight, have a strong family history of diabetes and have acanthosis nigricans, hypertension, dyslipidaemia or the polycystic ovarian syndrome. Testing in these individuals should be done at least every 2 years starting from age 10 years or at the onset of puberty, if the latter occurs at a younger age (pg 109).

Grade B, Level IIa

C Children and adolescents with impaired glucose tolerance and obesity should be managed with diet and exercise (pg 111).

Grade C, Level IV

C Children with type 2 diabetes mellitus may initially be treated with lifestyle modifications (diet and exercise), unless they are symptomatic or severely hyperglycaemic (pg 110).

Grade C, Level IV

C Oral hypoglycaemic agents may be started in children with type 2 diabetes if glycaemic targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control (pg 110).

Grade C, Level IV

Prevention of Type 2 Diabetes

A Individuals at high risk for developing diabetes should be made aware of the benefits of even modest weight loss and participating in regular physical activity (pg 116).

Grade A, Level Ib

B Screening for high risk individuals should be done opportunistically, with either a fasting plasma glucose test, or a 2-hour OGTT (pg 114).

Grade B, Level IIb

A Persons with impaired glucose tolerance or impaired fasting glucose should be given counselling about weight loss as well as instructions on how to increase physical activity (pg 116).

Grade A, Level Ib

C Drug therapy should not be routinely used to prevent diabetes until more information, particularly in regard to cost-effectiveness, is available (pg 116).

Grade C, Level IV

Clinical Quality Indicators for Diabetes Mellitus

A Measures of process of diabetes care should include the initial and ongoing performance of medical indicators which have been proven to influence long-term outcome (pg 122).

Grade A, Level Ib

GPP Data to measure the outcomes of diabetes management should be obtained from the individual with diabetes (pg 122).

GPP

1 Introduction

1.1 Development of guidelines

The first edition of the MOH clinical practice guidelines on diabetes mellitus for Singapore was published in 1999. Since that time, more facts about this important condition have emerged, not only with regard to its diagnosis and treatment, but also about whether or not type 2 diabetes may be prevented, and, if so, how this may be achieved.

As diabetes mellitus has great public health significance in developed countries and developing nations alike, managing it properly involves a consideration, not just of clinical issues, but also of health economics. This second edition of the guidelines attempts to address some of these complex issues wherever evidence-based information pertaining to them is available.

1.2 Objectives

The main aim of these guidelines is to help physicians make sound clinical decisions about diabetes mellitus by presenting up-to-date information about diagnosis, classification, treatment, outcomes, and follow-up.

These guidelines are developed for all health care professionals in Singapore. We hope they would be helpful especially to primary care physicians who care for patients with diabetes mellitus.

1.3 What's new in the revised guidelines

The following is a list of the major revisions and additions to the previous guidelines:

- The diagnosis of diabetes mellitus and other categories of glucose tolerance underwent a significant change in 1997/1998. In late 2003, the American Diabetes Association proposed another new modification to the diagnostic criterion for impaired fasting glucose (IFG). Chapter 2 addresses this, and presents an update on how clinicians should diagnose and screen for diabetes and glucose intolerance.

- Chapter 5 on pharmacotherapy in diabetes mellitus has been updated to take into account recent clinical trial evidence of the efficacy of the newer classes of antidiabetes drugs.

- Chapter 7 on prevention of cardiovascular disease in diabetes mellitus has been extensively revised to address clinical targets for blood pressure and lipids. Recommendations on decision-making in the area of therapeutics have also been updated.

- Chapter 8 on prevention and management of diabetic nephropathy has been revised to present recent clinical trial evidence regarding the efficacy of, and indications for, the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

- Chapter 9 on the prevention and management of eye complications has been updated. Additionally, the new guidelines include a set of colour plates of retinal photographs (Annex 1, page 151). We hope the visual information these plates present would help physicians recognize diabetic retinal disease more readily, and take the appropriate clinical actions.

- Chapter 11 on pregestational and gestational diabetes mellitus has been updated.

- Chapter 12 on childhood and adolescent diabetes mellitus has new data on the appropriate use of biguanides in these patient groups.

- Chapter 13 is a new chapter that addresses prevention of type 2 diabetes mellitus. It reviews important information arising out of recent clinical trials designed to find out if type 2 diabetes mellitus could be prevented.

- Chapter 14 addresses cost-benefit issues in diabetes mellitus.

- Chapter 15 provides an update on clinical quality indicators for diabetes. Patients with diabetes are catagorised into 'at risk' and' 'high risk' individuals and recommended frequency to measure different quality indicators is specified for each category e.g HbA_{1c} should be measured 6 monthly for 'at risk' and 3-4 monthly for 'high risk' diabetes patients.

- A new section on self-assessment containing 10 multiple choice questions has been added.

1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review four years after publication, or earlier if new evidence emerges that necessitates substantive changes to the recommendations.

2 Diagnosis and Screening of Diabetes Mellitus in Singapore

2.1 Introduction

In the 2004 National Health Survey,[1] diabetes mellitus (DM) was found to affect 8.2% of our population. In 2004, it was the 8th most common cause of death in Singapore.[2] It is associated with considerable mortality and morbidity from chronic complications. In Singapore, it is associated with a 3-fold increase in mortality, most of which is related to cardiovascular disease.[3]

Early diagnosis and aggressive treatment of DM and its associated metabolic derangements (hyperglycaemia, dyslipidaemia, hypertension and obesity) can prevent or delay the progression of the major chronic complications including both macrovascular disease (coronary heart disease)[4-8] and microvascular disease (retinopathy, nephropathy, neuropathy).[9,10] It is therefore important to detect individuals with DM so that appropriate therapeutic measures can be taken to minimize the morbidity caused by this devastating disease. At the same time, when a diagnosis of DM is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and life-long.

2.2 Objective

It is the objective of the workgroup to provide recommendations regarding the screening and diagnosis of DM that are appropriate for our population. To achieve this, the workgroup closely examined the recommendations of the American Diabetes Association[11] (ADA) and the World Health Organization[12] (WHO), the European Diabetes Epidemiology Group[13] and the International Diabetes Federation.[14] In addition, we took into account data derived from our own population.[15]

The recommendations are summarised in Table 1 (page 23). Figures 1 and 2 (pages 24 and 25) are flow charts showing a recommended diagnostic strategy.

2.3 Diagnosis of diabetes mellitus

The recommendations for the diagnosis of diabetes mellitus remain unchanged from the previous MOH clinical practice guideline (4/99).

In the presence of unequivocal hyperglycaemia with acute metabolic decompensation (e.g. diabetic ketoacidosis, hyperosmolar non-ketotic hyperglycaemic coma), DM can be diagnosed without further testing. In the patient with typical symptoms, DM can be diagnosed on any one of the following criteria:

1) casual plasma glucose ≥11.1 mmol/l,
2) fasting plasma glucose (FPG) ≥7.0 mmol/l, or
3) 2-hour post-challenge plasma glucose (2hPG) ≥11.1 mmol/l.

In other individuals, it is recommended that a second plasma glucose value in the diagnostic range be obtained on a separate day before the individual is labeled diabetic. If a second sample fails to confirm the diagnosis, periodic re-testing is recommended in accordance with the recommendations for screening of asymptomatic individuals.

Fasting is defined as no consumption of food or beverage except water for at least 8 hours. Casual plasma glucose refers to plasma glucose at any time of the day, without regard to the interval since the last meal. The 1-hour post-challenge glucose is not useful for the diagnosis of DM.

Because of its greater simplicity and greater reproducibility when compared to the 2hPG, the FPG is the preferred diagnostic test. However, from local data, we have found that the use of FPG ≥7.0 mmol/l alone would result in the classification of 39.1% of subjects with 2hPG ≥11.1 mmol/l as non-diabetic. Therefore, we recommend that all subjects with FPG from 6.1 to 6.9 mmol/l be subjected to an oral glucose tolerance test (OGTT) to determine the glycaemic status precisely.[16]

Until such time that adequate standardisation of glycated haemoglobin is available, the latter should not be used routinely for the diagnosis of DM. Urine glucose testing for the diagnosis of DM is not recommended.

2.4 Other categories of glucose tolerance

Both the ADA and the WHO recognize states of glucose metabolism intermediate between normal glucose tolerance and DM. In addition to impaired glucose tolerance (IGT), an intermediate category based on the FPG, termed impaired fasting glucose by the ADA[11] and impaired fasting glycaemia by the WHO,[12] is recognised. These two intermediate categories represent an increased risk for the development of DM[17-20] and cardiovascular disease.[3,15,21,22]

In 1997, the ADA recommended that subjects with FPG 6.1 to 6.9 mmol/l be classified as "impaired fasting glucose".[23] The WHO recommended that individuals with FPG from 6.1 to 6.9 mmol/l be subjected to OGTT where possible and that "impaired fasting glycaemia" be diagnosed if the OGTT reveals a FPG from 6.1 to 6.9 mmol/l and 2hPG <7.8 mmol/l (Table 2, page 23).[12] In the 1999 MOH clinical practice guideline, we recommended the adoption of the WHO classification for Singapore. This recommendation has not changed.

In late 2003, the ADA recommended that the lower limit for impaired fasting glucose be further lowered from 6.1 mmol/l to 5.6 mmol/l. This was predicated on the belief that this lower level better predicts future diabetes mellitus and cardiovascular disease.[11] The committee has examined the data and arguments for and against the adoption of this new cut-off point for the diagnosis of impaired fasting glucose.[13] We believe that the benefits of the adoption of this new cut-point are uncertain at this time. As such, we recommend against the adoption of the ADA recommendation.

2.5 Screening of asymptomatic individuals

The workgroup recommends that screening be carried out for subjects at increased risk of diabetes mellitus. These recommendations have been addressed in the MOH Clinical Practice Guidelines for Health Screening (6/2003). The workgroup accepts all these screening guidelines, but recommends lowering the cut-off value of triglycerides at which the individual is considered at increased risk of diabetes to harmonize screening and targets for control.

Screening of asymptomatic individuals at high risk for type 2 diabetes mellitus should be carried out on an opportunistic basis.

Screening should begin at age 40 years, and be considered at an earlier age (e.g. 30 years) if risk factors for diabetes are present. Subsequently, screening should be carried out every three years for those with normal glucose tolerance and annually for those with impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT).

Risk factors for diabetes include:

- Overweight/obesity (body mass index ≥25.0 kg/m^2)
- Hypertension (≥140/90 mmHg)
- A first degree relative with diabetes mellitus
- Previous gestational diabetes mellitus
- Coronary heart disease
- Polycystic ovary disease
- Dyslipidaemia (HDL cholesterol <1.0 mmol/l, and/or triglyceride level ≥2.30 mmol/l)*
- Previously identified impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT).

* Note that the triglyceride level has been lowered from 2.82 mmol/l in the MOH Clinical Practice Guidelines on Health screening to 2.30 mmol/l.

Special considerations regarding the collection and measurement of plasma glucose for the diagnosis and screening of diabetes mellitus.

1) We wish to emphasise that the aforementioned recommendations are based on plasma glucose measured in an accredited laboratory.
2) Plasma (collected with anticoagulants) glucose and serum (collected without anticoagulants) glucose can differ by as much as 5%.[24] Today, many routine biochemical measurements are made using serum samples. Therefore, in a subject whose glucose concentration is close to the diagnostic cut-off (e.g. 6.5-7.5 mmol/l), the physician should clarify that the test was carried out using plasma and not serum. If not, one should consider repeating the diagnostic test in an appropriately collected plasma sample.
3) Plasma glucose will decline if the blood sample is not processed within 60 minutes of blood collection.[25] A tube containing a glycolytic inhibitor such as sodium fluoride should be used for collecting the sample if the blood cannot be processed within 60 minutes.
4) Glucometers are suitable for the evaluation of glycemic control to evaluate adequacy of therapy. Glucometers should not be used for the diagnosis of diabetes mellitus.

Table 1 Diagnostic criteria for diabetes mellitus

Diagnose diabetes mellitus if one of the following is present:

Casual[b] plasma glucose	≥11.1 mmol/l
Fasting[c,d] plasma glucose	≥7.0 mmol/l
2-hour plasma glucose during an oral glucose tolerance test[e]	≥11.1 mmol/l

Important notes to diagnosis:

a. In the absence of typical symptoms or unequivocal hyperglycaemia with acute metabolic decompensation, a second confirmatory test must be done in all cases on another day. Any one of the above three methods may be used for the second confirmatory test, but fasting plasma glucose is the diagnostic test of choice.
b. Casual is defined as any time of the day, without regard to the interval since the last meal.
c. Fasting is defined as no calorie intake for at least 8 hours.
d. Fasting plasma glucose rather than an oral glucose tolerance test is the preferred diagnostic test.
e. Oral glucose tolerance test (75 g glucose) should be performed in accordance to WHO recommendations.
f. Venous blood samples should be collected in appropriate tubes for plasma glucose measurement, which should be performed in accredited laboratories. Results obtained from finger prick capillary blood samples measured by portable glucose meters should not be considered as a diagnostic procedure even if confirmed on another occasion.

Table 2 Intermediate categories of glucose tolerance

	Fasting plasma glucose		2-hour plasma glucose
Impaired Fasting Glycaemia	6.1-6.9	and	<7.8
Impaired Glucose Tolerance	<7.0	and	7.8-11.0

The workgroup recommends the adoption of the criteria from the WHO consultation. All subjects with fasting plasma glucose from 6.1-6.9 mmol/l should undergo a 75 g oral glucose tolerance test.

Figure 1 Flowchart for the diagnosis of diabetes mellitus

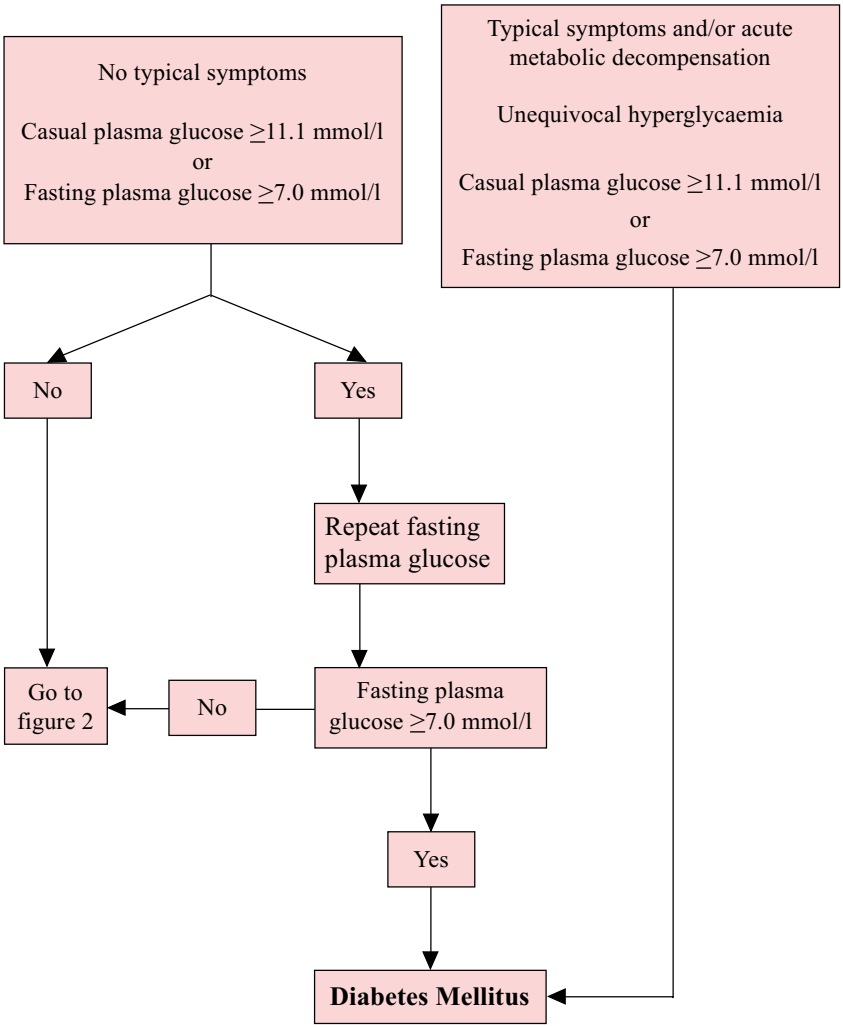
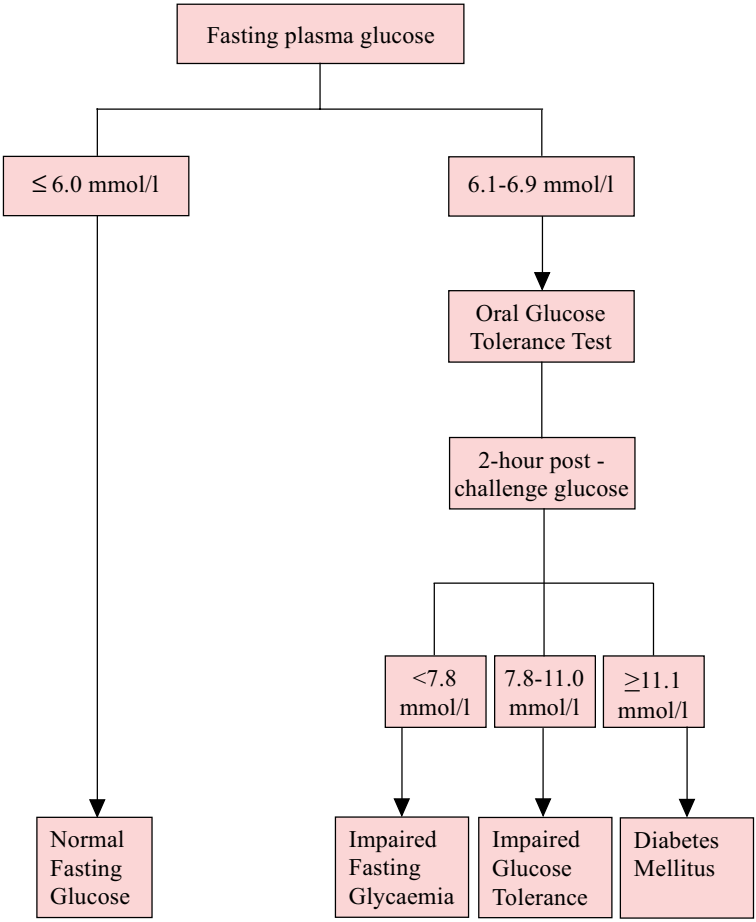


Figure 2 Flowchart for individuals suspected to have diabetes but whose fasting plasma glucose <7.0 mmol/l



2.6 Summary of key recommendations

B In subjects with unequivocal hyperglycaemia with acute metabolic decompensation, diabetes mellitus can be diagnosed without further testing.

Grade B, Level III

B In patients with typical symptoms, diabetes mellitus can be diagnosed if any one of the following is present:

1. Casual plasma glucose ≥11.1 mmol/l
2. Fasting plasma glucose ≥7.0 mmol/l
3. 2-hour post-challenge glucose ≥11.1 mmol/l

Other individuals should have a repeat test on a subsequent day.

Grade B, Level III

B Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus.

Grade B, Level III

B We should recognise intermediate states of glucose metabolism termed impaired fasting glycaemia and impaired glucose tolerance in accordance with the report of the WHO consultation.

Grade B, Level III

B All subjects with fasting plasma glucose from 6.1 to 6.9 mmol/l should undergo a 75 g oral glucose tolerance test to determine if they have impaired glucose tolerance or diabetes mellitus.

Grade B, Level III

C Screening of asymptomatic individuals for diabetes mellitus should be carried out in accordance with the Ministry of Health Clinical Practice Guidelines for Health Screening (6/2003).

Grade C, Level IV

N.B. The workgroup recommends lowering the cut-off value of triglycerides at which the individual is considered at increased risk of diabetes from 2.82 mmol/l in MOH clinical practice guidelines on health screening to 2.3 mmol/l.

3 Classification of Diabetes Mellitus

3.1 Definition of diabetes

Diabetes mellitus is a heterogenous metabolic disorder characterized by presence of hyperglycaemia. The chronic hyperglycaemia of diabetes mellitus is associated with long-term sequelae resulting from damage to various organs especially kidney, eye, nerves, heart and blood vessels.

3.2 Classification

The first widely accepted classification of diabetes was published by the National Diabetes Data Group (NDDG) in 1979 and the World Health Organisation (WHO) Expert Committee on Diabetes Mellitus in 1980. They recognized 2 major forms of diabetes mellitus:-

a) Insulin-dependent diabetes mellitus (IDDM, type 1 diabetes)

b) Non insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes)

This classification terminology of IDDM-NIDDM has often caused confusion as it was based on the type of pharmacological treatment. The American Diabetes Association (ADA) in 1997[23] and the WHO Consultation in 1998,[12] proposed the following changes to the NDDG/WHO 1979/1980 Classification:

a) The various types of diabetes mellitus are defined based on aetiology.

b) The terms *type 1* and *type 2* are retained (note Arabic rather than Roman numerals) and the terms *IDDM* and *NIDDM* are eliminated.

c) Classification is according to aetiologic types:
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Gestational diabetes
- Other specific types

Type 1 diabetes

Characterised by β-cell destruction which

(i) is attributable to an autoimmune process, i.e. *immune mediated type 1,* or

(ii) may not have a known aetiology, i.e. *idiopathic type 1.*

Markers for type 1 immune-mediated diabetes include autoantibodies to islet cell (ICAs), insulin (IAAs), glutamic acid decarboxylase (GAD), and tyrosine phosphatases IA-2 and IA-2β.

In Europoids, the majority of type 1 diabetes is immune-mediated. Type 1 idiopathic is more common among Africans and Asians. In Singapore, autoantibodies to GAD and/or ICAs were detectable in 40% of type 1 diabetes, and in the remaining 60%, no autoimmune markers were found.[26]

Immune-mediated type 1 diabetes commonly occurs in childhood and adolescence but can occur at any age, even in the 8th and 9th decades of life. Some patients, particularly children and adolescents, may present with ketoacidosis or with an acute dramatic onset of hyperglycaemia. Adults, however, may present in a manner resembling type 2, but progress quickly to insulin-requiring state.

Although patients are rarely obese, the presence of obesity is not incompatible with the diagnosis. These patients may also have other autoimmune disorders - such as Graves' disease, Hashimoto's thyroiditis and Addison's disease.

Type 2 diabetes

Characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time the diabetes is manifest. The specific reasons for the development of defects in insulin action and secretion are not completely elucidated.

Type 2 diabetes is the most common form of diabetes. Its frequency varies in different racial/ethnic subgroups. It often has a strong familial and genetic predisposition. In Singapore, prevalence rates in adults aged >30

years was reported to be 12.0%. It is estimated that >90% of persons with diabetes mellitus have type 2 diabetes.[27-29]

The risk of developing type 2 diabetes is associated with increasing age, obesity and lack of physical activity. It occurs more frequently in women with prior gestational diabetes and in individuals with hypertension and dyslipidaemia.

Type 2 diabetes is frequently undiagnosed for many years because hyperglycaemia develops gradually and at earlier stages, it is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications.

These individuals initially, and often throughout their lifetimes, do not need insulin for survival. However, people with type 2 diabetes may require insulin treatment at some stage of their disease. Ketoacidosis is infrequent and usually arises in association with the stress of another illness such as infection.

Gestational diabetes (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. It does not exclude the possibility that glucose intolerance may have predated the pregnancy but had been previously unrecognised. The definition applies irrespective of whether insulin is used for treatment, or whether the condition persists after pregnancy.

Women who become pregnant and are known to have diabetes mellitus which antedates their pregnancy do not have GDM, but have “diabetes mellitus and pregnancy” or “pregestational diabetes”.

The diagnosis and management of GDM, and management of women with diabetes and pregnancy, are detailed in Chapter 11 - “Management of women with pregestational and gestational diabetes mellitus”.

Other specific types

This refers to those relatively uncommon causes of diabetes in which the underlying defect or disease process can be specifically identified e.g. genetically defined forms of diabetes, or those associated with other diseases or drug use.

3.3 Summary

Diabetes mellitus is classified according to aetiological types:

I. Type 1 diabetes mellitus (β-cell destruction, usually leading to absolute insulin deficiency)
   - Immune mediated
   - Idiopathic

II. Type 2 diabetes mellitus (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)

III. Gestational diabetes mellitus (onset or recognition of glucose intolerance in pregnancy)

IV. Other specific types (conditions in which the underlying defect or disease process is specifically defined)

4 Lifestyle Modification

4.1 Introduction

Lifestyle modification is a cornerstone of diabetes management and comprises the following:

- medical nutrition therapy
- physical activity and exercise
- avoidance of smoking

Medical nutrition therapy and exercise prescription should be the initial therapy in obese (BMI $\geq$ 30.0) and overweight (BMI $\geq$ 25.0) type 2 diabetic patients unless they are symptomatic or severely hyperglycaemic.[30]

4.2 Medical nutrition therapy

There is clear evidence that weight loss and dietary modification in obese type 2 diabetics can restore normal carbohydrate metabolism.[30] If weight reduction is needed, it should be attempted gradually (0.25 to 1.0 kg/week).[31] In type 1 diabetes, the main effort should be directed towards dietary manipulation and insulin therapy to improve glycaemic control.[32]

The diet plan must be appropriate to the patient's activity status, cultural and ethnic practices, and dietary habits. Special attention should be paid to the patient's dietary requirements during periods of sickness, travel and exercise.[32-34] The diet should include foods from each of the basic food groups. The saturated fat intake should be decreased to less than 10% of total calories, carbohydrates 50% to 60% of total calories and protein 15 to 20% of total calorie intake respectively. The diet should also contain adequate vitamins and minerals.[32-34]

The cholesterol content of the diet should be <300 mg per day.[32-34] Daily consumption of a diet containing 20-35 g of dietary fibre from a wide variety of food sources is recommended.[35] Sodium intake should be restricted to <2 g per day for individuals with hypertension.[32-34] Patients with poor glycaemic control or overweight diabetics should abstain from alcohol.[32-34] The use of alternative

sweeteners (i.e. aspartame, saccharin) is acceptable within the recommended safety limit.[32]

4.3 Physical activity and exercise

An exercise programme should be prescribed for each individual patient to suit his age, aptitude, fitness and interest. A pre-exercise evaluation which includes a full medical history and examination to identify macrovascular, microvascular and neurological complications is recommended for the patient with diabetes.[32-34] For patients over 40 years of age and/or with high risk of coronary heart disease intending to do more than low intensity exercise such as walking, an exercise stress electrocardiogram is indicated.[32-34]

The guidelines for exercise are as follows[32-34]:

- Frequency : 3-5 days per week (daily if low intensity)
- Intensity : 60-85% of maximum heart rate (till patient feels warm or sweats and breathes deeply).
- Time : 20-60 minutes each time, fairly continuously.
- Type : aerobic exercises like walking, jogging, swimming, cycling, ball and racket games; combined with light callisthenic exercises.

For subjects who have not been active for some time, low intensity activities like walking should be started first for at least 4-6 weeks, initially for 10-15 minutes, gradually increasing in duration up to 60 minutes.

Precautions for patients with diabetes during exercise include[32-34]:

- Use of proper footwear and other appropriate protective equipment
- Adequate hydration before, during and after prolonged exercise
- Avoidance of heavy resistance and isometric exercises
- Avoidance of exercise during periods of severe hyperglycaemia and hypoglycaemia in type 1 diabetes (e.g. when blood glucose is above 15 mmol/l or below 3 mmol/l)

Individuals with diabetes, especially those on insulin treatment, should receive specific education on the prevention of exercise-induced hypoglycaemia. The following measures may help prevent exercise-induced hypoglycaemia:

- Reduce medication prior to exercise (i.e. insulin in type 1 diabetic patients, insulin or oral antihyperglycaemic agents in type 2 diabetic patients in whom glycaemic control has been optimised).
- Consume some carbohydrate 30-60 minutes before exercise especially if blood glucose is <5.5 mmol/l, and after every 30 minutes of moderately intense exercise.
- Gradual progression of exercise intensity.
- Administer insulin into a site away from the most actively exercising extremities.

Additional precautions should be undertaken for the following individuals with complications:

- in patients with sensory neuropathy, exercises with significant potential for skin, joint and/or bone injuries such as prolonged walking, jogging, running, treadmill, step exercises and contact sports should be avoided.
- in patients with severe diabetic retinopathy, activities that dramatically elevate blood pressure such as weight-lifting, heavy Valsalva maneuvers, and heavy competitive sports should be undertaken with caution.

4.4 Avoidance of smoking

Individuals with diabetes should be discouraged from smoking. Nicotine promotes both macrovascular and microvascular disease in individuals with diabetes. A large number of prospective studies have shown the major impact of smoking on morbidity and mortality and the benefits of smoking cessation.[36-38]

4.5 Alcohol

Diabetic patients with poor blood glucose control or other medical problems like pancreatitis, dyslipidaemia or neuropathy should be discouraged from consuming alcoholic beverages.[32,33,35]

4.6 Summary of recommendations

B Lifestyle modification is a cornerstone of diabetes management. Medical nutrition therapy and exercise prescription should be the initial therapy in obese (BMI $\geq$ 30) and overweight (BMI $\geq$ 25) type 2 diabetic patients unless they are symptomatic or severely hyperglycaemic.

Grade B, Level IIa

C Medical nutrition therapy should be individualised. Saturated fat intake should not exceed 10%, with carbohydrates 50-60% and proteins 15-20% of total calorie intake. Diet should include foods from each of the basic food groups.

Grade C, Level IV

C An exercise programme tailored to suit the individual's age, fitness, aptitude and interest should be prescribed.

Grade C, Level IV

C A pre-exercise evaluation to identify macrovascular, microvascular and neurological complications is recommended.

Grade C, Level IV

C Individuals with diabetes, especially those on insulin treatment, should receive specific education on the prevention of exercise-induced hypoglycaemia.

Grade C, Level IV

C Individuals with diabetic neuropathy should avoid exercises associated with repetitive foot trauma.

Grade C, Level IV

C Individuals with severe diabetic proliferative retinopathy should avoid activities that dramatically elevate blood pressure.

Grade C, Level IV

B Individuals with diabetes should be discouraged from smoking.

Grade B, Level III

B Diabetic patients with poor glycaemic control or dyslipidaemia should be discouraged from consuming alcohol.

Grade B, Level IIb

5 Pharmacotherapy in Diabetes Mellitus

5.1 Introduction

The primary goal of diabetes therapy is to maintain general health so as to allow the person with diabetes to lead a normal and active lifestyle. Specifically, this includes both the avoidance of acute complications (hyperglycaemic and hypoglycaemic emergencies) and chronic vascular complications.

All type 1 diabetic patients need insulin treatment. Type 2 diabetes is treated with oral agents when diet and exercise fail to control glycaemia.[39] Additionally, type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes.[40] Stepwise therapy with multiple pharmacological agents is often needed over time to maintain target glucose control. Two or more oral agents, or insulin therapy either alone or in combination with oral agents, may be required.[41] Therefore, it is important to remember that frequent refinement of the therapeutic regime is often necessary in order to attain the targets of glycaemic control, i.e. the practitioner needs to consider stepping up or down pharmacotherapy as glycaemic control changes.

Although type 1 diabetic patients typically present with an acute, dramatic onset, some may present in a manner more resembling type 2 diabetes. These patients, however, progress quickly to an insulin-requiring state. Therefore, the possibility that a non-obese adult patient may have rapid β-cell failure (i.e. latent autoimmune diabetes in adults, or LADA) and thus requires insulin replacement, must always be carefully considered.[42]

The optimal treatment of type 2 diabetes should be based on a sound understanding of its pathophysiology. It is believed that impaired insulin action at metabolically active tissues (i.e. skeletal muscle, adipose tissue and hepatocytes)[43] and pancreatic β-cells[44] constitutes the primary defect in glucose intolerance. This is known as insulin resistance (IR). It is believed that adipocytes secrete proteins (adipocytokines e.g. tumour necrosis factor-α, resistin) that profoundly influence insulin action.[45] Initially, there is compensatory pancreatic β-cell insulin hypersecretion in response to IR. As long as the compensatory hyperinsulinaemia is adequate, euglycaemia is maintained. In susceptible individuals, β-cell decompensation occurs after some time, thereby resulting in

hyperglycaemia. First phase insulin response is affected first, resulting in postprandial hyperglycaemia. With progressive β-cell failure, fasting hyperglycaemia ensues because hepatic glucose output, which is normally attenuated by insulin, is increased. In addition, insulin resistance at the level of adipocytes leads to increased lipolysis and release of free fatty acids. These free fatty acids result in further insulin resistance at the muscle level as well as further impairment of insulin secretion at the pancreatic level.[46] Hence, when a subject presents with diabetes, multiple defects in metabolism have already been established.

5.2 Oral antihyperglycemic agents

Currently approved oral agents for the treatment of type 2 diabetes in Singapore include insulin secretagogues (sulphonylureas, meglitinides), biguanides, alpha-glucosidase inhibitors and thiazolidinediones. Insulin secretagogues, which include sulphonylureas[47] (tolbutamide, chlorpropamide, glibenclamide, glipizide, gliclazide, glimepiride) or non-sulphonylureas[48] (nateglinide, repaglinide) stimulate pancreatic insulin release. Biguanides (metformin) decrease hepatic glucose release, enhance peripheral glucose disposal and delay glucose absorption.[49] Alpha-glucosidase inhibitors (acarbose) slow the digestion and absorption of starch and sucrose in the gut, thereby reducing the increase in postprandial blood glucose.[50] Thiazolidinediones (rosiglitazone and pioglitazone) enhance tissue sensitivity to insulin in muscle and liver through activation of intracellular receptors.[51,52] Sulphonylureas may increase the risk of hypoglycaemia, but this effect is not commonly seen with metformin, alpha-glucosidase inhibitors or thiazolidinediones unless combined with insulin or sulphonylureas.

5.3 Guidelines for oral agent therapy

The cornerstones of therapy for type 2 diabetes remain medical nutritional therapy, exercise and education. Patients may initially be treated with lifestyle modification (diet and exercise) for 2 to 4 months unless they are symptomatic or severely hyperglycaemic. Oral antihyperglycaemic agents should be started if glycaemic targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control. If glycaemic targets are not reached with a single oral agent, combination therapy with one or more agents (including insulin) from other classes may be considered. However, one would need to monitor carefully for adverse events such as hypoglycaemia or fluid retention.

The choices of oral drug therapy for type 2 diabetes have become extremely complex. The physician must use good clinical judgement about the best combinations for the patient with diabetes.

The following points should be considered in the choice of the oral agent:[53]

1. Age of patient

The risks of medications are often increased with advancing age. For instance, decline in renal function is often not reflected in a measurable change in serum creatinine because of an accompanying decline in muscle mass. Metformin, which must be used with care in renal impairment, should hence be used with caution in elderly patients. In addition, decline in cardiac function and risks of volume overload in the elderly may become clinically apparent with the use of thiazolidinediones. In elderly patients, initiating therapy with low-dose, short-acting oral antihyperglycemic agents is recommended. Metformin is the only oral antihyperglycemic agents approved by FDA for use in children with type 2 diabetes.

2. Weight of patient

In overweight patients, metformin is the oral agent of first choice as it causes less weight gain than sulphonylureas. Because of the significant insulin resistance associated with obesity, metformin and thiazolidinediones may be particularly useful.

3. Renal impairment

The use of certain oral hypoglycaemic agents in renal impairment, especially long-acting drugs like glibenclamide and chlorpropamide, may increase the risk for hypoglycaemia. Metformin is usually contraindicated in the presence of renal or hepatic insufficiency as it may cause lactic acidosis. Thiazolidinediones may cause fluid retention, particularly in patients with renal dysfunction.

4. Cardiopulmonary comorbidities

Metformin must be used with care in the presence of co-morbid conditions which increase the risks of lactic acidosis (e.g. class III or IV cardiac failure). Thiazolidinediones need to be used with caution in subjects at risk of fluid retention (e.g. cardiac failure).[54]

5. Hepatic disease

Hepatic insufficiency increases the risks of lactic acidosis and hypoglycaemia and influences the metabolism of many oral antihyperglycemic agents.

The mechanism of action, advantages and disadvantages of major classes of oral antihyperglycemic agents are shown in Table 3 (page 39).[55] Two algorithms for oral hypoglycaemic agents are shown in Figures 3 and 4 (pgs 40 and 41).[56]

5.4 Combination therapy

Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes. Stepwise therapy with multiple pharmacological therapies is often needed over time to maintain target glucose control. Two or more oral agents, or insulin therapy either alone or in combination with oral agents, may be required.

Since there are almost always multiple defects in type 2 diabetes, the early institution of combination therapy targeting these derangements is an attractive option. However, the cost-effectiveness of this approach has not yet been well studied.

Table 3 Currently available oral therapeutic options for type 2 diabetes mellitus

Sulfonylureas (SUs)	Non-SU Secretagogues	Biguanides	α-Glucosidase Inhibitors	Thiazolidinediones
Mechanism of action				
Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Decreased hepatic glucose production	Decreased gut carbohydrate absorption	Increased peripheral glucose disposal
Advantages				
Well established Decreases microvascular risk Convenient daily dosing	Targets postprandial glycaemia Possibly less hypoglycaemia and weight gain than with SUs	Well established Weight loss No hypoglycaemia Decreases microvascular risk Nonglycemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia) Convenient daily dosing	Targets postprandial glycaemia No hypoglycaemia Nonsystemic	No hypoglyacemia Reverses prime defect of type 2 diabetes Nonglycemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia, improved endothelial function) Possible β-cell preservation Convenient daily dosing
Disadvantages				
Hypoglycaemia Weight gain Hyperinsulinemia (effect of this uncertain)	More complex (3 times daily) dosing schedule Hypoglycaemia Weight gain No long-term data Hyperinsulinemia (effect of this uncertain)	Adverse gastrointestinal effects Many contraindications Lactic acidosis (rare)	More complex (3 times daily) dosing schedule Adverse gastrointestinal effects No long-term data	Liver function test monitoring Weight gain Oedema Slow onset of action No long-term data
Food and Drug Administration approval status				
Monotherapy Combination with insulin, metformin, thiazolidinedione, α-glucosidase inhibitors	Monotherapy Combination with metformin	Monotherapy Combination with insulin, SU, non-SU secretagogue, thiazolidinedione	Monotherapy Combination with SU	Monotherapy Combination with insulin (rosiglitazone at ≤4 mg daily or pioglitazone), SU, metformin

Figure 3 Management algorithm for non-obese type 2 diabetes mellitus

It is recommended that each treatment is allowed 6 weeks to work before stepping up therapy.

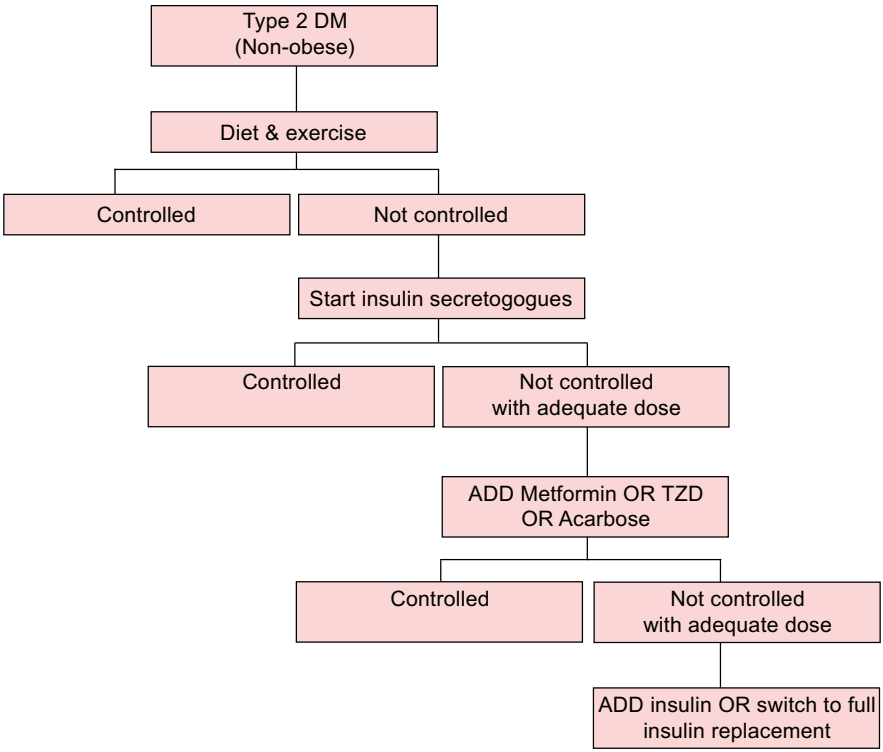
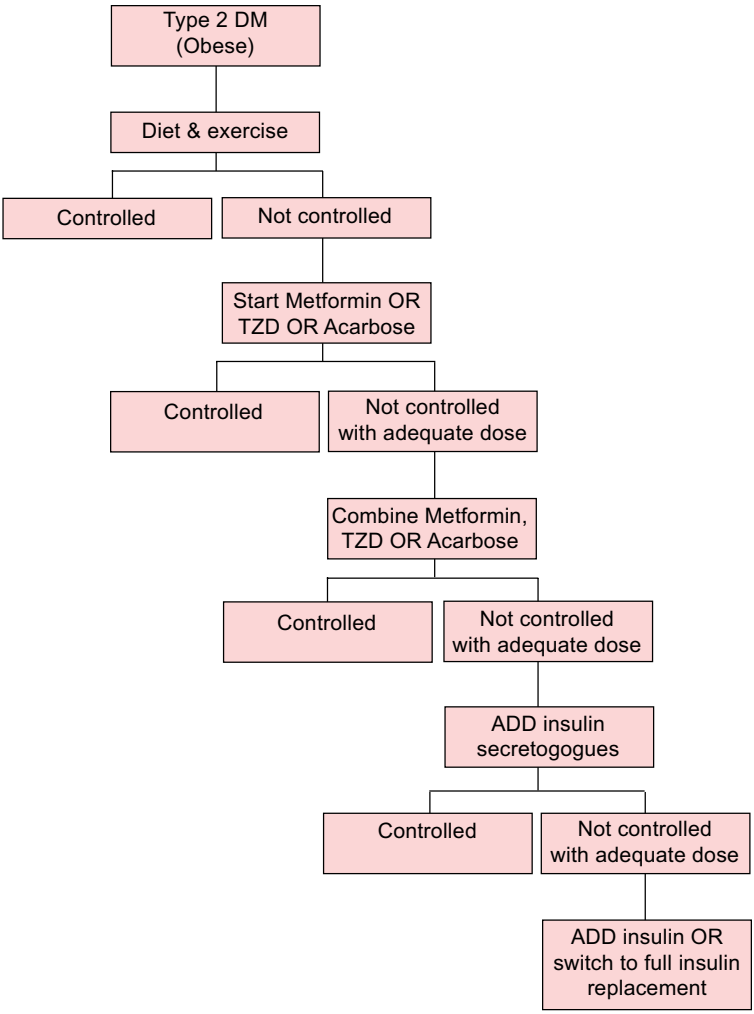


Figure 4 Management algorithm for obese type 2 diabetes mellitus

It is recommended that each treatment is allowed 6 weeks to work before stepping up therapy.



5.5 Insulin therapy

Insulin replacement therapy is required for all people with type 1 diabetes and for many with type 2 diabetes. In the latter, insulin may also be used temporarily to control hyperglycaemia during acute illness or stress. Newer insulin therapies, including the concept of physiologic basal-bolus insulin and the availability of insulin analogues, are changing clinical diabetes care. The key to effective insulin therapy is an understanding of principles that, when implemented, can result in improved diabetes control. Unfortunately, tight glycaemic control is associated with a certain degree of risk of hypoglycaemia.

Patients on insulin must be equipped not only with the skills of insulin administration, but also should be educated on self-monitoring of blood glucose, hypoglycaemia management and dose adjustments during sick days, travel, exercise, and changes in food intake.

5.6 Guidelines for insulin treatment

Some of the more common insulin regimens include the following:

- Twice-daily administration of one of the following regimens:
  - short-acting insulin (regular/soluble insulin) or rapid-acting insulin analogue (insulin lispro or aspart), with intermediate-acting insulin (neutral protamine Hagedorn (NPH) or insulin zinc suspension (IZS) before breakfast and before dinner, or
  - pre-mixed regular and NPH insulins before breakfast and before dinner, or
  - pre-mixed rapid-acting insulin analogues and their protaminated intermediate-acting analogues (protaminated insulin lispro or protaminated insulin aspart) before breakfast and dinner.

- Multiple daily injections (three or more) using short-acting insulin or rapid-acting insulin analogues before meals with intermediate-acting or long-acting insulin at bed-time (basal-bolus regimen).

- A single injection of intermediate-acting insulin or long-acting insulin/ insulin analogue at bedtime combined with daytime oral agents for selected type 2 diabetic patients.

Many premixed insulin preparations (stable mixtures of fixed proportions of rapid-acting insulin analogues with protaminated insulin analogues, or short-acting insulin with intermediate-acting insulin) are available commercially. Insulin is also available in cartridges for use in special insulin pens for easy storage, dosing and administration. The pharmacological characteristics of various types of insulins differ from each other. Insulin type and species, injection technique, site of injection and insulin antibodies can all affect the onset, degree, and duration of insulin activity. Intensive insulin therapy using an insulin pump (e.g. continuous subcutaneous insulin infusion or CSII) is an alternative to multiple daily injections, primarily in patients with type 1 diabetes.[10] Because of residual β-cell secretory capacity, insulin therapy regimens used in type 2 diabetic patients may be less complicated than those prescribed for patients with type 1 diabetes, although fairly similar regimens are also used in type 2 diabetics who become totally dependent on insulin.

5.7 Rapid-acting insulin analogues

Three rapid-acting insulin analogues, insulin lispro, aspart, and insulin glulisine have been developed. These demonstrate faster absorption kinetics and can therefore be injected just before meals. They also attain higher concentrations after subcutaneous injection compared to conventional human insulin and reduce post-prandial glucose to a greater extent.[57,58,59] The shorter duration of action of these rapid-acting insulin analogues also leads to a lower incidence of hypoglycaemia. These insulin analogues may hence be considered for patients in whom tight glycaemic control with standard insulin regimens has resulted in severe hypoglycaemia.

5.8 Long-acting insulin analogues

Two long-acting insulin analogues, insulin glargine and insulin detemir, are available for use locally.[60,61] These long-acting analogues have virtually no plasma peak, and act for about 24 hours,[62] hence allowing once-daily administration as basal therapy. The time of day at which these analogues are injected has no clinically relevant effect on glycaemic control. These

characteristics make them ideal to cover basal insulin requirement. These new long-acting insulin analogues may provide more predictable fasting blood glucose with lower intra-subject variation and reduced risk of hypoglycaemia compared with NPH. Patients on intermediate-acting and long-acting insulin who experience frequent hypoglycaemic episodes related to their peak activity may benefit from the use of insulin glargine which has been shown to achieve better glycaemic control with lower incidence of hypoglycaemia.[62]

5.9 Inhaled insulins

Inhaled insulins[63] have been in development for more than a decade. In early 2006, an inhaled form of human insulin, Exubera, was approved in Europe and the United States for the treatment of type 1 and 2 diabetes in adults. Both the FDA and the European Agency for the Evaluation of Medicinal Products have specified that the drug is contraindicated in smokers and in patients who have smoked in the preceding six months. It is not recommended in patients with asthma, bronchitis or emphysema. The drug's long term pulmonary safety is under study.

5.10 Insulin therapy in type 1 diabetes

All patients with type 1 diabetes require insulin. Achieving optimal glycaemic control via insulin replacement strategies (usually with multiple daily injections) designed to simulate the physiologic patterns of insulin secretion in response to 24-hour post-absorptive and postprandial glucose profiles is necessary to prevent or delay microvascular complications.[10]

Pre-meal soluble insulin or rapid-acting insulin analogue can be administered by multiple daily injections (MDI) or CSII. Once or twice daily intermediate-acting insulin or long-acting insulin or long-acting insulin analogue may be added to a MDI regimen for optimal glycemic control.

5.11 Insulin therapy in type 2 diabetes

In type 2 diabetes, management using oral agents should be complemented, or replaced, with insulin therapy depending on disease progression and development of secondary failure of oral agents. Decisions to introduce insulin therapy to type 2 diabetic patients are often predicated on their inability to achieve target HbA_{1c} levels after a duration of about 6 months or so, despite good compliance with optimal oral antidiabetic regimens coupled with weight control and exercise programmes. In certain situations, intensive insulin therapy may even be required. As in type 1 diabetes, intensive insulin therapy may prevent and delay progression of microvascular complications in individuals suffering from type 2 diabetes mellitus.[64]

Introduction of insulin should not be delayed if metabolic control becomes suboptimal.[65] This may be initiated as a bedtime dose of intermediate-acting or long-acting insulin with maintenance of oral agents during the day, an approach frequently termed bedtime insulin and daytime sulfonylurea or BIDS for short.[66] In patients with satisfactory fasting and pre-meal blood glucose levels but elevated post-dinner or bedtime readings, using premixed regular and intermediate-acting insulin pre-dinner may prove more effective than intermediate-acting insulin at bedtime. The advantages of BIDS include improved glycaemic control with a smaller dose of insulin and therefore less weight gain than pure insulin therapy.[67]

When glycaemic control is not achieved despite BIDS regimen, discontinuing sulphonylureas and switching to basal-bolus insulin regimen becomes necessary. However, metformin[68] and thiazolidinediones[54] or α-glucosidase inhibitors[69] may still be used in conjunction with exogenous insulin to attenuate the insulin dose. Fine-tuning of insulin doses is best determined by home blood glucose monitoring. Type 2 diabetes subjects who are switched to insulin temporarily during episodes of acute stress, such as sepsis, may be put back on oral agents when their glycaemic control improves with declining insulin resistance and glucotoxicity.[70]

5.12 Summary of recommendations

A Type 2 diabetic patients may initially be treated with lifestyle modification (diet and exercise) for 2 to 4 months unless they are symptomatic or severely hyperglycaemic (i.e. random blood glucose >15 mmol/l or fasting blood glucose >10 mmol/l). Oral antihyperglycaemic agents should be started, if glycaemic targets are not achieved. Insulin therapy should be started, if optimal combination therapy fails to attain target control (i.e. 2 consecutive HbA_{1c} values failed to reach ≤8% over 3-6 months interval).

Grade A, Level Ia

A Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes. Stepwise therapy with multiple pharmacological therapies is often needed over time to maintain target glucose control. Two or more oral agents, or insulin therapy, either alone or in combination with oral agents, may be required.

Grade A, Level Ia

A All type 1 diabetic patients must receive insulin. Multiple daily injections (3 or more) or the use of continuous subcutaneous insulin infusion (CSII or insulin pump therapy) may be required to achieve target glucose levels.

Grade A, Level Ib

Table 4 Insulin types

Insulin Types		Onset	Peak	Duration
Rapid-acting insulins	Human insulin analogues:			
	1) Insulin lispro (Humalog)	5-15 mins	1-2 hours	3-5 hours
	2) Insulin aspart (NovoRapid)	10-20 mins	1-3 hours	3-5 hours
Short-acting insulins	Recombinant human regular insulin:			
	1) (Humulin R)	30-60 mins	2-4 hours	6-8 hours
	2) (Actrapid)			
Intermediate-acting insulins	NPH (Humulin N or Insulatard)	1-4 hours	8-12 hours	12-20 hours
	Lente (Humulin L or Monotard)			
Long-acting insulins	1) (Humulin U)	3-5 hours	10-16 hours	18-24 hours
	2) (Ultratard)	3-5 hours	10-16 hours	18-24 hours
	3) Insulin glargine (Lantus)	1-4 hours	peakless	24 hours
	4) Insulin detemir (Lemevir)	1-4 hours	peakless	18-24 hours
Premixed Insulins	1) (Mixtard 30 or Humulin 30/70): premixed 30% regular insulin + 70% intermediate-acting insulin	30-60 mins	2-8 hours	24 hours
	2) (Mixtard 50 or Humulin 50/50): premixed 50% regular insulin + 50% intermediate-acting insulin	30-60 mins	2-8 hours	24 hours
	3) Biphasic insulin analogue - (NovoMix 30): premixed 30% insulin aspart + 70% protaminated insulin aspart	10-20 mins	1-3 hours	24 hours
	- (Humalog Mix 25/75): premixed 25% insulin lispro + 75% protaminated insulin lispro	10-20 mins	1-3 hours	24 hours

6 Glycaemic Control: Assessment and Targets

6.1 Introduction

Monitoring of glycaemic status is regarded as a cornerstone of diabetes care. It provides information to help physicians and patients make adjustments to diabetes treatment. Prospective randomised controlled trials like the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) have shown that improved glycaemic control is associated with sustained decreased rates of retinopathy, nephropathy and neuropathy.[9,10,71] Glycaemic control is assessed by monitoring of blood glucose, and measuring glycated haemoglobin.

6.2 Blood glucose testing by patients

Self-monitoring of blood glucose (SMBG) by patients should be an integral part of diabetes self-care since the information obtained may be used to guide therapy and assess the efficacy of treatment. SMBG also serves as a useful educational tool to improve patient compliance and participation in diabetes self-care.[72-74]

GPP Health care professionals should be familiar with the practical use of glucometers.

GPP

Indication for SMBG:

SMBG is indicated for the following types of patients[72-74]:

- All insulin-treated patients
- All pregnant patients with pre-existing diabetes or gestational diabetes
- Non insulin-treated patients who are at increased risk of developing hypoglycaemia and/or are vulnerable to injury from hypoglycaemia
- All patients who have failed to achieve glycaemic goals

Frequency of SMBG:

The frequency of SMBG is as follows:

- For patients with type 1 diabetes, daily monitoring is recommended.[10] The frequency and timing of glucose monitoring should be dictated by the needs and goals of each individual patient, but for most type 1 diabetic patients, SMBG is recommended 3 or 4 times daily. Some patients may need to perform SMBG at 2 am or 3 am if there are hypoglycaemic symptoms such as nervousness, tremulousness, giddiness or sweatiness in the night.
- The optimal frequency of SMBG for non-insulin treated type 2 diabetic patients is not known, but it should be frequent enough to facilitate reaching glucose targets. For insulin-treated type 2 diabetic patients, testing 2 or 3 times a day on two to three days a week would be appropriate.
- For patients with unstable metabolic control, changes in daily routine, alterations of treatment regimens or intercurrent illness, the frequency of SMBG should be increased.
- Daily self monitoring of blood glucose appears to be superior to intermittent office monitoring of plasma glucose in pregnant patients with diabetes.

Methodology and accuracy

Visual method:

GPP The visual method of SMBG is not recommended.

GPP

Although the visual method of SMBG is economical, it is semi-quantitative and highly operator-dependent.With the price of glucometers and test strips coming down, the visual method is not to be recommended.

Glucometer:
With improved technology, most brands of glucometers in the market today are reliable and robust. However, the accuracy of glucometers is highly operator-dependent. It is important for health care professionals to evaluate each patient's monitoring technique, both initially and at regular intervals. Common errors are: inadequate amount of blood sample, using defective or expired test strips, incorrect calibration, forgetting to calibrate, and

instrument failure. Most glucometers are designed to test capillary whole blood (i.e. blood from the finger). Slightly higher results may be observed when using venous samples, due to differences in the way the electrodes react to venous and capillary whole blood. Some glucometers calibrate blood glucose readings to plasma values. Plasma glucose values are 10-15% higher than whole blood glucose values. Users should know whether their glucometer and strips provide whole blood or plasma results. In general, caution should also be exercised in interpreting values in the hypoglycaemia (<2.0 mmol/l) and severe hyperglycaemia (>20.0 mmol/l) ranges.

Initial training for the use of blood glucometers should be provided by qualified staff i.e. nurses, doctors or pharmacists rather than asking the patient to follow the manufacturer's manual. To ensure optimal benefit from SMBG, patients must be educated on the interpretation of glucose levels.[73] Periodic reviews are recommended to verify users' competency, together with comparisons between results from patient self-testing of blood glucose in the clinic and simultaneous laboratory testing. It is also recommended that calibration checks of meters be periodically conducted using standard solutions according to the manufacturer's recommendations.

New blood glucose monitoring systems

The recent introduction of near-continuous glucose monitors in some countries represents an advance that may be particularly useful in the management of patients with type 1 diabetes. However, these devices measure interstitial glucose concentrations, not blood glucose or plasma glucose. There is currently insufficient data to suggest that these methods are reliable or robust enough to replace SMBG, or be used on a wide scale.

6.3 Self-monitoring of urine

Self-monitoring of urine glucose

C Testing for glucose in urine is not recommended for monitoring of glycaemic status.

Grade C, Level IV

Urine glucose testing is simple and inexpensive to perform. However, the accuracy of such tests is influenced by the high variability of the renal

threshold for glucose. Furthermore, urine glucose testing provides no information about blood glucose levels below the renal threshold and does not detect hypoglycaemia.[75] Due to these limitations, urine glucose testing is not recommended.

Self-monitoring of urine ketones

Testing for urinary ketone is an important part of monitoring in patients with type 1 diabetes, pregnancy with pre-existing diabetes, and gestational diabetes.[76] In appropriate circumstances, the presence of ketones in the urine may indicate impending metabolic decompensation and the development of ketoacidosis.

C Testing for ketones in the urine is recommended in patients with type 1 diabetes, pregnancy with pre-existing diabetes, and gestational diabetes, if there is[76]:

- Acute illness or stress
- Persistent elevation of blood glucose (>16.7 mmol/l)
- Any symptom suggestive of ketoacidosis (nausea, vomiting, abdominal pain or acetone breath)

Grade C, Level IV

Testing of blood ketones

GPP Routine monitoring of blood ketones is not recommended for type 1 or type 2 diabetic patients.

GPP

Blood ketone kits are now available. These quantify β-hydroxybutyric acid, the predominant ketone body. Blood ketone testing may be superior to urine ketone testing for diagnosing and monitoring ketoacidosis.[76] There is currently insufficient evidence to recommend routine monitoring of blood ketones for diabetic patients, whether type 1 or type 2.

6.4 Glycated haemoglobin

Methodology

The measurement of glycated haemoglobin (HbA_{1c}) quantifies average glycaemia over the previous 2-3 months, thereby complementing blood glucose testing which provides information on day-to-day glycaemic excursions. The glycated haemoglobin has been shown to predict the risk

for development of microvascular complications such as diabetic retinopathy and nephropathy. As many different types of glycated haemoglobin assay methods are available in the clinical laboratory, doctors ordering the test should be aware of the assay method used, the glycated components measured (HbA_1 or HbA_{1c}), the non-diabetic reference interval, and potential assay interferences.[77]

Frequency of testing

C The following schedule is recommended for glycated haemoglobin testing[77]:

- 3- to 4-monthly in patients with unstable glycaemic control, failure to meet treatment goals, recent adjustment in therapy, or intensive insulin therapy.
- 6-monthly in patients who have stable glycaemic control and who are meeting treatment goals.

Grade C, Level IV

6.5 Targets of glycaemic control

Rationale

When its findings were first announced in 1993, the Diabetes Control and Complications Trial (DCCT) provided conclusive evidence of the relationship between elevated blood glucose levels and microvascular complications in patients with type 1 diabetes.[10] Continued follow up of DCCT subjects revealed tight glucose control lowered the risk of a cardiovascular disease event by 42 percent and the risk of a serious event, including heart attack or stroke, by 58 percent.[78] A prospective study similar in design to DCCT but involving fewer subjects showed a comparable reduction in microvascular complications in lean Japanese subjects with type 2 diabetes.[79] The UK Prospective Diabetes Study (UKPDS) showed that intensive blood glucose control by either sulphonylureas or insulin substantially decreased the risk of microvascular disease in patients with type 2 diabetes.[9] Based on the above studies, a 1% decrease in absolute HbA_{1c} value correlates to a 35-60% reduction in risk for microvascular complications.

Patients striving to achieve the best level of glucose control they can achieve may encounter hypoglycaemia. This has been shown in clinical studies which clearly demonstrate an increased risk of hypoglycaemia

in "intensive" treatment groups that aim for near-normal glycaemic control.[9,10,79] Therefore glycaemic targets must be individualised to ensure that patients do not incur an undue risk of hypoglycaemia or other hazards associated with tight control.[80] The risk of severe hypoglycaemia in type 2 diabetic patients, however, is generally lower than that in type 1 diabetic patients on intensive therapy.

Defining targets of glycaemic control

The targets of glycaemic control should be defined for each patient, with patient participation in the process (see Table 5, page 54).[31]

"Ideal"

This refers to HbA_{1c} levels within the normal range (4.5-6.4%). This level of glucose control may not always be attainable by the majority of patients with diabetes. However, this is the desired target for pregnant women with pre-existing diabetes or gestational diabetes. There is a small body of recent evidence that suggests that HbA_{1c} levels decrease during normal pregnancy. This may be of importance in future when defining the goal for HbA_{1c} for pregnant women with pre-existing diabetes or gestational diabetes.[81]

"Optimal"

This refers to HbA_{1c} levels (6.5-7.0%) that approach the normal range and is associated with a significantly reduced risk of developing chronic microvascular complications, as shown by the DCCT[10] and UKPDS[9] results. This is the desirable target of control for the majority of patients with diabetes.

"Suboptimal"

This refers to HbA_{1c} levels (7.1-8.0%) that are attainable in the majority of patients with diabetes. However, patients with HbA_{1c} results in this category should be encouraged to lower glucose levels further toward optimal levels. In special subsets of patients, this suboptimal level of glucose control may be the best that is safely attainable (see below).

"Unacceptable"

This refers to HbA_{1c} levels >8.0%, and glucose levels that may be associated with acute metabolic decompensation and/or complications of hyperglycaemia. Patients with glucose levels within this range require

reassessment and readjustment of therapy, and referral to the diabetes care team if no improvement occurs.

Factors modifying glycaemic targets

Although adult patients with diabetes should aim for at least an "optimal" level of glucose control, "suboptimal" control may be adequate in the following circumstances:

- Older patients with significant atherosclerosis who may be vulnerable to permanent injury from hypoglycaemia.
- Patients with severe diabetes-related complications or co-morbidities (e.g. severe coronary artery disease, cerebrovascular disease, renal failure, proliferative retinopathy, advanced autonomic neuropathy) who may be at increased risk for hypoglycaemia and/or vulnerable to permanent injury from hypoglycaemia.
- Preadolescent children (who may have unpredictable eating schedules or highly variable activity levels, and who may not adhere to treatment schedules) may be at increased risk for hypoglycaemia.

Table 5 Targets of glycaemic control

Test	Assessment of Glucose Control			
	Ideal (non-diabetic levels)	**Optimal (target goal for majority of patients)**	**Suboptimal (adequate goal for some patients)‡**	**Unacceptable (action needed in all patients)**
HbA_{1c}* (%)	4.5 - 6.4	6.5 - 7.0	7.1 - 8.0	>8.0
Pre-meal glucose† (mmol/l)	4.0 - 6.0	6.1 - 8.0	8.1 - 10.0	>10.0
2-hour post-meal† glucose (mmol/l)	5.0 - 7.0	7.1 - 10.0	10.1 - 13.0	>13.0

Notes:

* Normal reference range obtained from NUH and SGH laboratories using Biorad Variant II^{R}. Other laboratories should establish their own non-diabetic reference intervals.

† Values pertaining to capillary blood sample.

‡ Adequate goal in elderly patients and individuals with advanced diabetic complications or other co-morbidities.

6.6 Summary of recommendations

GPP Health care professionals should be familiar with the practical use of glucometers.

GPP

B Self-monitoring of blood glucose (SMBG) should be initiated in most patients with diabetes, especially in insulin-treated subjects, in pregnant women with pre-existing diabetes or gestational diabetes, and in patients who are at increased risk of developing hypoglycaemia.

Grade B, Level IIa

GPP The visual method of SMBG is not recommended for self-monitoring of blood glucose.

GPP

A Besides receiving proper training in the use of blood glucometers, patients must be educated on the interpretation of the results and, where possible, taught to modify treatment according to blood glucose levels.

Grade A, Level Ib

C Testing for glucose in urine is not recommended for monitoring of glycaemic status.

Grade C, Level IV

C Testing for ketones in the urine is recommended in patients with type 1 diabetes, pregnancy with pre-existing diabetes, and gestational diabetes, if there is:

- Acute illness or stress
- Persistent elevation of blood glucose (>16.7 mmol/l)
- Any symptom suggestive of ketoacidosis (nausea, vomiting, abdominal pain or acetone breath)

Grade C, Level IV

GPP Routine monitoring of blood ketones is not recommended for type 1 or type 2 diabetic patients.

GPP

C Glycated haemoglobin (HbA_{1c}) testing should be performed routinely in all patients with diabetes. The frequency of testing for any individual patient may vary according to the treatment regimen used and the status of glycaemic control.

Grade C, Level IV

C The following schedule is recommended for glycated haemoglobin testing:

- 3- to 4-monthly in patients with unstable glycaemic control, failure to meet treatment goals, recent adjustment in therapy, or intensive insulin therapy.
- 6-monthly in patients who have stable glycaemic control and who are meeting treatment goals.

Grade C, Level IV

C The targets of glycaemic control should be defined for each patient, with patient participation in the process.

Grade C, Level IV

A "Optimal" glucose control should be the target for the majority of patients with diabetes. This refers to glucose levels that approach the normal range (HbA_{1c} 6.5-7.0%; preprandial glucose 6.1-8.0 mmol/l) and is associated with a low risk of developing microvascular complications.

Grade A, Level Ib

A "Suboptimal" glucose control (HbA_{1c} 7.1-8.0%; preprandial glucose 8.1-10.0 mmol/l) may be the target in special subsets of patients who are vulnerable to injury from the increased risk of severe hypoglycaemia associated with "optimal" glucose control.

Grade A, Level Ib

7 Prevention of Cardiovascular Disease in Diabetes Mellitus

7.1 Introduction

Type 2 diabetes mellitus has been identified as a major risk factor for atherosclerotic disease. In Singapore, almost 60% of subjects with diabetes mellitus die as a consequence of cardiovascular disease (CVD).[3] Furthermore, case-fatality is higher in subjects with type 2 diabetes mellitus. As many as 50% of persons suffering their first myocardial infarction die, and never become eligible for measures intended for secondary prevention.[82] Therefore, the primary prevention of CVD is a major goal of therapy in type 2 diabetes mellitus.

Apart from hyperglycaemia, persons with type 2 diabetes mellitus often have several other abnormalities including hypertension, dyslipidaemia, a prothrombotic state, endothelial dysfunction, a pro-inflammatory state, and obesity. This chapter deals primarily with aspects that are critical to therapeutic decision-making in the clinical setting.

7.2 Assessment of risk of cardiovascular disease in type 2 diabetes mellitus

Type 2 diabetes mellitus should be considered a coronary heart disease (CHD) risk equivalent.[83] As such, additional risk stratification is not necessary.

However, since atherosclerosis in type 2 diabetes mellitus is multifactorial in nature, an assessment of the CVD risk factors present is recommended for all persons with type 2 diabetes mellitus in order that appropriate therapy be instituted.

GPP The assessment of cardiovascular risk in persons with type 2 diabetes mellitus should include:

1. A medical history, which should include:
   a. A smoking history.
   b. A history of hypertension and/or medication taken for the treatment of hypertension.

c. A history of pre-existing CVD to include angina pectoris, myocardial infarction, stroke, or peripheral vascular disease.

2. A physical examination which should include an assessment of peripheral pulses.
3. Blood pressure should be measured each time a patient with type 2 diabetes mellitus is seen in the clinic.
4. Fasting serum lipids should be measured at the time of diagnosis and at least once a year if they are in the optimal range.
5. Assessment of urine for microalbuminuria or proteinuria should be carried out at the time of diagnosis and at least once a year in all patients.
6. In view of the fact that persons with type 2 diabetes mellitus are more likely to experience atypical symptoms of coronary heart disease (CHD), a routine resting ECG is recommended at baseline. Subsequent ECG may be performed when clinically indicated. Specific abnormalities which may suggest CHD should be assessed by a cardiologist for appropriate risk stratification.

GPP

7.3 Measures to prevent cardiovascular disease in persons with type 2 diabetes mellitus

The prevention of CVD in persons with type 2 diabetes mellitus must take a global approach with intervention targeting all aspects of the disease.[84]

While optimising glycaemic control may have a greater impact on reducing the risk of microvascular complications compared to CVD,[9,10] attempts to manage hyperglycaemia must be continued.

7.4 The role of therapeutic lifestyle modification in reducing the risk of cardiovascular disease associated with type 2 diabetes mellitus

Therapeutic lifestyle modification (through modulation of diet and physical activity) should form the mainstay of strategies to reduce CVD risk associated with type 2 diabetes mellitus. Such therapeutic lifestyle modification should include the following:

1) Smoking. All possible efforts should be taken to encourage persons with type 2 diabetes mellitus to stop smoking. These measures include counselling and behavioral measures. In some instance, these measures may be used in conjunction with pharmacological agents that improve smoking cessation rates.
2) Medical nutrition therapy. In addition to the maintenance of an optimal body weight and optimising of glycaemic control, the goals of medical nutrition therapy should include optimisation of the lipid profile and blood pressure.
3) Increased physical activity will improve cardiovascular fitness in addition to improving other aspects of cardiovascular risk including dyslipidaemia, obesity and hypertension.

7.5 Management of hypertension in persons with type 2 diabetes mellitus

Hypertension is common in persons with type 2 diabetes mellitus. The presence of hypertension is associated with increased risk of microvascular complications (retinopathy and nephropathy) as well as macrovascular complications (stroke, CHD, and peripheral vascular disease).

Goals of therapy and levels for the initiation of pharmacologic therapy

The blood pressure target in persons with type 2 diabetes mellitus should be <130/80 mmHg.[6,84-87]

Implementing treatment for hypertension in persons with type 2 diabetes mellitus

Lifestyle modification and drug therapy should be instituted for all subjects with blood pressure (BP) exceeding 130/80 mmHg.

Recent studies[6,88] have shown that the most important issue in the treatment of hypertension is achieving goal BP levels expeditiously.

There is a general agreement on the principles concerning the use of antihypertensive drugs to lower BP that is independent of the choice of any particular drugs. These principles include:

- Use low doses of drugs to initiate therapy, beginning with the lowest available dose of the particular drug, with the aim of reducing adverse effects.
- If there is a significant response to a low dose of a single drug but the BP is still above target levels, one could either increase the dose of the same drug, provided that this is well tolerated, or add a low dose of a second drug from a different class.
- There are advantages of adding a low dose of a second drug rather than increasing the dose of the original drug. This allows both the first and the second drug to be used in the low dose range that is more likely to be free of side effects. In this context, the use of fixed low dose combinations that are available may be considered.[89]
- Use appropriate drug combinations to achieve target BP levels if this cannot be achieved by one single antihypertensive agent.
- Use of appropriate drug combinations enables BP lowering efficacy to be maximised while minimising side effects. In most patients, appropriate combination therapy produces BP reductions that are twice as great as those obtained with monotherapy (e.g. magnitude of reduction increases from 12 to 22 mmHg in systolic BP and from 7 to 14 mmHg in diastolic BP in patients with an initial BP of 160/100 mmHg).
- Change to a different drug class altogether if there is poor tolerance to the first drug.
- In patients whose pretreatment BP is moderately elevated (e.g. BP $\geq$ 160/100 mmHg) or especially if it is severely elevated (e.g. BP $\geq$ 180/110 mmHg), it may be appropriate to begin with combination therapy, because many such patients will require 2 or even 3 drugs for adequate BP control.

Choice of pharmacologic therapy

There are five main classes of antihypertensive agents available in Singapore. They are:
(a) diuretics (D)
(b) β-blockers (BB)
(c) calcium channel blockers (CCB)
(d) ACE inhibitors (ACEI)
(e) angiotensin II receptor blockers (ARB).

These drug classes have been shown to be beneficial over placebo for the prevention of CVD in patients with type 2 diabetes mellitus.[6-8,85,86,90-94] The choice of first line therapy can include any of these agents and should be based on the cost of the drug and any compelling indications and contraindications for their use (Table 6 below). There are other classes of drugs which are now uncommonly used, such as the alpha-blockers, hydralazine and methyldopa.

Table 6 Guidelines for selecting drug treatment of hypertension[95]

Concomitant Conditions	Recommended Drugs	Contraindicated Drugs
Heart Failure	D, ACEI, ARB	CCB*
Angina	BB, CCB	
Post Myocardial Infarction	BB, ACEI, ARB	
Isolated Systolic Hypertension	D, CCB, ACEI, ARB	
Diabetes Mellitus with Proteinuria (micro or macroalbuminuria)	ACEI, ARB	
Diabetes Mellitus	ACEI, ARB, CCB, D, BB	
Post-Stroke	D, ACEI	
Asthma & Chronic Obstructive Pulmonary Disease		BB
Heart Block		BB, CCB*
Gout		D
Bilateral Renal Artery Stenosis		ACEI, ARB

* *verapamil or diltiazem*

Source: Ministry of Health. Clinical Practice Guidelines on Hypertension. MOH, Singapore:2005.

In hypertensive patients who do not have compelling indications or contraindications for any particular drug, any of the above 5 classes of drugs can be considered as the initial therapy.

7.6 Management of dyslipidaemia in persons with type 2 diabetes mellitus

All persons with type 2 diabetes mellitus should have a full lipid profile, including LDL-C, fasting triglyceride and HDL-C, measured at the time of diagnosis. These should be obtained after 10-12 hours of fasting. If optimal, serum lipids should be measured 6- to 12-monthly.

Goals of therapy in the management of dyslipidaemia

The goals of lipid lowering therapy in persons with type 2 diabetes mellitus are found in Table 7 below.

Table 7 Goals of lipid lowering therapy in type 2 diabetes mellitus

Lipid measurement	Goal level
LDL cholesterol	<2.6 mmol/l (100 mg/dl)
Triglyceride	<2.3 mmol/l (200 mg/dl)
HDL cholesterol	≥1.0 mmol/l (40 mg/dl)

In all diabetic patients, a goal for LDL-C of <2.6 mmol/l (100 mg/dl) is strongly recommended.

Recently, the results of two large trials comparing the lowering of LDL-C to < 2.6 mmol/l (100 mg/dl) versus very low LDL-C of around 2.1 mmol/l (80 mg/dl) in patients with pre-existing CHD were announced.

The Treating to New Targets Study (TNT)[96] compared 80 mg with 10 mg of atorvastatin in patients with CHD. There was a lower incidence of acute myocardial infarction and stroke in the 80 mg atorvastatin group whose on-treatment mean LDL-C level was 2.0 mmol/l (77 mg/dl) compared to the 10 mg atorvastatin group whose on-treatment mean LDL-C level was 2.6 mmol/l (101 mg/dl). However, the total mortality was similar in both groups.

In the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL)[97] study, 80 mg of atorvastatin was compared to 20-40 mg of simvastatin in patients with previous acute myocardial infarction. There was a lower incidence of non-fatal myocardial infarction and coronary revascularization in the 80 mg atorvastatin group whose on-treatment mean LDL-C level was 2.1 mmol/l (81 mg/dl) compared to the 20-40 mg simvastatin group whose on-treatment mean LDL-C level was 2.7 mmol/l (104 mg/dl). However, the total mortality was similar for both groups.

Based on these data, in a very high risk patient (i.e. diabetic patient with pre-existing CHD), an "optional goal" of LDL-C < 2.1 mmol/l (80 mg/dl) may be considered[96,97] by the physician who, however, must balance the benefits against the cost and potential side-effects of high doses of medication, or combination therapy which are often required to achieve very low levels.

Priorities for the treatment of dyslipidaemia in persons with type 2 diabetes mellitus

For the prevention of CHD, the first priority is optimization of the LDL cholesterol. This is followed by HDL-cholesterol, and then triglyceride. The exception is in individuals with levels of TG >4.5 mmol/l (400 mg/dl) who have an increased risk of acute pancreatitis. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis.

Choice of pharmacologic therapy

Fibrate therapy should be considered as first line therapy for those with TG > 4.5 mmol/l (400 mg/dl) to prevent acute pancreatitis.[98]

For all other type 2 diabetic patients with LDL-C >2.6 mmol/l (100 mg/dl), the drug of choice is an HMG CoA reductase inhibitor (statin).[4] This should be started concurrently with therapeutic lifestyle modification.[99] The statin should be titrated upwards to achieve the LDL goal. Statins also have moderate efficacy in the reduction of serum triglyceride and raising HDL cholesterol level.

If HDL cholesterol remains low (<1.0 mmol/l or 40 mg/dl) after achieving the LDL goal with a statin, combination therapy can be considered in selected high risk patients, such as those with type 2 diabetes mellitus and

existing CHD.[100] The combination of a statin with a fibrate is associated with increased risk of myositis. When combining a statin with a fibrate, gemfibrozil should not be used. This is because gemfibrozil has been shown to adversely alter the pharmacokinetics of a statin when used in combination with the latter.[101] This effect is not seen with fenofibrate.[102, 103]

Based on the results of the VA-HIT study, patients with established CHD whose primary lipid abnormality is a low HDL-C despite lifestyle changes can be given a fibrate to elevate the HDL-C level.[104]

In all dyslipidaemias where a fibrate is recommended, nicotinic acid can also be considered. A recent multi-centre VA study[105-107] showed that low-dose (2-3 g/day) crystalline nicotinic acid significantly improved atherogenic dyslipidaemia without an adverse effect on glycaemic control.

7.7 Management of the prothrombotic state in persons with type 2 diabetes mellitus

Type 2 diabetes mellitus is a prothrombotic state which may predispose affected individuals to CVD. Aspirin therapy has been found to be useful in both primary and secondary prevention of CVD in patients with type 2 diabetes mellitus.[6,108,109] The recommended dose for maximum efficacy with minimum side effects lies between 75 and 325 mg per day.[110] The workgroup recommends that all patients over the age of 45 years or who have concomitant hypertension, dyslipidaemia or pre-existing CVD (CHD, stroke or peripheral arterial disease) should be treated with aspirin 75-100 mg per day. In the presence of aspirin allergy, other antiplatelet agents such as clopidogrel (75 mg per day) may be a reasonable alternative for patients with high risk.[111]

7.8 Prevention of cardiovascular disease in type 1 diabetes mellitus

Although no randomised controlled trials have examined CVD reduction in type 1 diabetes mellitus, it is likely that the reduction of CVD risk factors, as per type 2 diabetes mellitus, would also reduce the incidence of CVD in type 1 diabetes mellitus.[112-114] The workgroup recommends that the guidelines for patients with type 2 diabetes apply to type 1 diabetes.

7.9 Conclusions

Type 2 diabetes mellitus is a major risk factor for CVD. Global risk assessment is an essential part of the management of patients with type 2 diabetes mellitus. Special attention should be paid to smoking cessation and the management of hypertension, dyslipidaemia and the pro-thrombotic state. Multiple risk factor reduction has been shown to dramatically reduce the risk of cardiovascular disease in persons with type 2 diabetes mellitus.

7.10 Summary of key recommendations

GPP The assessment of cardiovascular risk in persons with type 2 diabetes mellitus should include:

1. A medical history, which should include:
   a. A smoking history.
   b. A history of hypertension and/or medication taken for the treatment of hypertension.
   c. A history of pre-existing cardiovascular disease to include angina pectoris, myocardial infarction, stroke, or peripheral vascular disease.
2. A physical examination which should include an assessment of peripheral pulses.
3. Blood pressure should be measured each time a patient with type 2 diabetes mellitus is seen in the clinic.
4. Fasting serum lipids should be measured at the time of diagnosis and at least once a year if they are in the optimal range.
5. Assessment of urine for microalbuminuria or proteinuria should be carried out at the time of diagnosis and at least once a year in all patients.
6. In view of the fact that persons with type 2 diabetes mellitus are more likely to experience atypical symptoms of CHD, a routine resting ECG is recommended at baseline. Subsequent ECG may be performed when clinically indicated. Specific abnormalities which may suggest CHD should be assessed by a cardiologist for appropriate risk stratification.

GPP

B The primary prevention of CVD should form one of the major goals of therapy in the management of type 2 diabetes mellitus.

Grade B, Level III

B Type 2 diabetes mellitus should be considered a CHD risk equivalent.

Grade B, Level III

C An assessment of the CVD risk factors present is recommended for all persons with type 2 diabetes mellitus in order that appropriate therapy be instituted.

Grade C, Level IV

A The prevention of CVD in persons with type 2 diabetes mellitus must take a global approach with intervention targeting all aspects of the disease.

Grade A, Level Ib

C Therapeutic lifestyle modification (through modulation of diet and physical activity) should form the mainstay of strategies to reduce cardiovascular risk associated with type 2 diabetes mellitus.

Grade C, Level IV

B All possible efforts should be taken to encourage persons with type 2 diabetes mellitus to stop smoking.

Grade B, Level III

Hypertension in patients with diabetes mellitus

A The target of hypertension treatment in type 2 diabetes mellitus should be < 130/80 mmHg.

Grade A, Level Ib

A Lifestyle modification and drug therapy should be instituted for all subjects with blood pressure >130/80 mmHg.

Grade A, Level Ib

A The choice of first line therapy can include (a) diuretics (D) (b) β-blockers (BB) (c) ACE inhibitors (ACEI) (d) calcium channel blockers (CCB) (e) angiotensin II receptor blockers (ARB) and should be based on the cost of the drug and any compelling indications and contraindications for its use.

Grade A, Level Ib

Dyslipidaemia in patients with diabetes mellitus

A For the prevention of CHD, the first priority is optimization of the LDL cholesterol. This is followed by HDL-cholesterol and then triglyceride.

Grade A, Level Ia

C The exception is in individuals with levels of TG >4.5 mmol/l (400 mg/dl) who have an increased risk of acute pancreatitis.

Grade C, Level IV

C Fibrate should be considered as first line therapy for those with TG levels > 4.5 mmol/l (400 mg/dl) to prevent acute pancreatitis.

Grade C, Level IV

A For all other patients with type 2 diabetes mellitus and LDL cholesterol >2.6 mmol/l (100 mg/dl), the treatment of choice is an HMG CoA reductase inhibitor (statin).

Grade A, Level Ia

A For patients with LDL cholesterol <2.6 mmol/l (100 mg/dl) and low HDL-cholesterol (<40 mg/dl), a fibrate can be started as the initial lipid lowering therapy.

Grade A, Level Ib

C If HDL cholesterol remains low (<1 mmol/l or 40 mg/dl) after achieving the LDL goal with a statin, combination therapy can be considered in selected high risk patients, such as those with type 2 diabetes mellitus and existing CHD.

Grade C, Level IV

B When combining a statin with a fibrate, gemfibrozil should not be used.

Grade B, Level III

Anti-thrombotic agents in patients with diabetes mellitus

A All patients with type 2 diabetes mellitus over the age of 45 years or who have concomitant hypertension, dyslipidaemia or pre-existing CVD (CHD, stroke or peripheral arterial disease) should be treated with aspirin 75-100 mg per day. In the presence of contraindications for aspirin therapy, other antiplatelet agents such as clopidogrel may be a reasonable alternative for patients with high risk.

Grade A, Level Ia

8 Prevention and Treatment of Diabetic Nephropathy

8.1 Introduction

Diabetes is the leading cause of end stage renal disease in Singapore. It accounted for nearly half (47.2%) of incident causes of end stage renal disease (ESRD) in Singapore in 2000.[115] The escalation of treated ESRD in Singapore is largely due to diabetic nephropathy. The progressive rise of diabetic nephropathy as the principal cause of new cases of ESRD is a global phenomenon.[116] This growth is due to several reasons: an increase in the number of diabetic patients, an increasing acceptance of diabetic ESRD into many end stage replacement programmes around the world, and possibly because better management of the metabolic and vascular complications of the disease has enabled larger number of diabetic persons to enter renal replacement programmes.

The burden of diabetic kidney disease is significant, both on a community as well as on a personal level. Diabetes adversely affects survival even while the patient is on dialysis; it is associated with higher numbers of hospitalizations and greater co-morbidity. Nevertheless, therapy can delay the development and progression of renal disease, and reduce the burden upon renal replacement programmes. For therapy to be effective, it must be instituted early enough to reduce both microvascular and macrovascular complications.

8.2 Stages of kidney disease

Kidney disease develops in a similar, though not identical, fashion in type 1 and type 2 diabetes mellitus,[117] with progressive proteinuria heralding the development of nephropathy. Less commonly, however, renal dysfunction may occur in the absence of the classic progressive albuminuria.[118,119]

Microalbuminuria (defined as low levels of urine albumin from 30 to 299 mg/day or 20 to 199 μg/min) develops in 40% of type 1 diabetic patients about 5 years after initial presentation, usually in association with an initial rising glomerular filtration rate (GFR), and later a fall in GFR, together with progressive hypertension. Microalbuminuria, however, can occur from non-renal related conditions such as hyperglycaemia, fever, urinary

tract infections, or heart failure. When it is due to diabetic nephropathy, microalbuminuria is persistent. Without specific interventions, 80% will progress to a stage of clinical proteinuria over a period of 10 to 15 years, where the urine albumin levels are >300 mg/l. The natural progression upon reaching this phase is progressive hypertension, together with a progressive linear decline of the GFR which is variable amongst individuals (2 to 10 ml/min GFR loss per year). ESRD usually occurs in 50% of type 1 diabetes with overt nephropathy within 10 years, and in more than 75% by 20 years.

A higher proportion of type 2 diabetic patients may have proteinuria at the time of diagnosis of hyperglycaemia, as the onset of development of hyperglycaemia is usually not distinct like it is with type 1 diabetes. Without specific interventions, a smaller proportion (20-40%)[117] with microalbuminuria will progress to overt nephropathy, but only about 20% of these patients would have progressed to ESRD within 20 years.

The development of microalbuminuria highlights the potential development of renal complications. It is also a marker for increased cardiovascular morbidity and mortality. Therapy at this phase of disease aims not only to retard renal disease progression, but also to reduce the risk of cardiovascular disease.

8.3 Screening for diabetic kidney disease

C Screening for albuminuria should begin at 5 years after the diagnosis of type 1 diabetes; it should, however, begin immediately with the diagnosis of type 2 diabetes. Thereafter, screening for albuminuria should be done annually.[117,120]

Grade C, Level IV

GPP Serum creatinine should be measured at least annually.

GPP

Screening for microalbuminuria can be performed by three methods:

1) measurement of the albumin-to-creatinine ratio in a random spot collection;
2) 24-hour urine collection; and
3) timed (e.g. 4-hour or overnight) collection.

The first method is the easiest to perform in an office setting, and provides accurate information. First-void is best because of the known diurnal variation in albumin excretion. Microalbuminuria is said to be present if urinary albumin excretion is 30 to 299 mg/24-hour (equivalent to 20 to 199 μg/min on a timed specimen or 30 to 299 mg/g creatinine on a random spot sample) (see Table 8 below). Short-term hyperglycaemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevations in urinary albumin excretion. If assays for microalbuminuria are not readily available, screening with reagent strips (e.g. Micral) for microalbumin may be carried out, since they show acceptable sensitivity (95%) and specificity (93%) when carried out by trained personnel. As reagent strips only indicate concentration and do not correct for creatinine as the spot urine albumin-to-creatinine ratio does, they are subject to possible errors from alterations in urine concentration. All positive tests by reagent strips should be confirmed by more specific methods. There is also marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3- to 6-month period should show elevated levels before a patient is diagnosed having microalbuminuria. An algorithm for microalbuminuria screening is given.

If the test for microalbumin is negative, it should be repeated annually.

Table 8 Definitions of abnormal albumin excretion

	Spot collection	24-hour collections	timed collections
Category	(μg/mg creatinine)	(mg/24-hr)	μg/min
Normal	<30	<30	<20
Microalbuminuria	30-299	30-299	20-199
Clinical albuminuria	≥300	>300	≥200

Uncommonly, progressive renal dysfunction can occur in small groups without the development of proteinuria.[112,113] The serum creatinine should be checked annually, and the estimated GFR calculated with one of several known formulae (Table 9, page 72).

Table 9 Estimation of glomerular filtration rate[121]

Cockcroft-Gault equation (where the creatinine is in mg/dl)

$$\text{Creatinine clearance} = \frac{(140\text{-Age}) \times \text{Weight (in kg)} \; (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine}}$$

or

MDRD formula (creatinine in mg/dl)

$$\text{Creatinine clearance} = 186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \; (\times 0.742 \text{ if female})$$

8.4 Therapy

Therapy to retard progression of renal disease includes measures to tighten glucose control, measures to control blood pressure, cessation of smoking, and a low protein diet.

8.5 Glycaemic control

Tight glycaemic control in both type 1 and type 2 diabetes mellitus can prevent the development of microalbuminuria and its progression to overt nephropathy.

The Diabetes Control and Complications Trial[10] demonstrated that type 1 diabetic patients reduced their risk of development or progression of retinopathy, nephropathy and neuropathy by 50 to 70% when intensively treated to an HbA_{1c} of 7.2% versus 9.0% in the conventionally treated group. Similarly in the United Kingdom Prospective Diabetes Study of type 2 diabetes mellitus, improved glycaemic control was associated with sustained decreased rates of retinopathy, nephropathy, and neuropathy.

8.6 Blood pressure control

C The blood pressure target in all persons with diabetes should be less than 130/80 mmHg. Diabetic patients with proteinuria levels exceeding 1 gram should try to have their BP lowered to less than 125/75 mmHg.[122]

Grade C, Level IV

Hypertension is common in patients with diabetes, especially in the presence of nephropathy. The prevalence of hypertension doubles when compared to non-diabetic populations; it may be present in up to 85% of diabetic subjects with overt nephropathy. Uncontrolled hypertension is associated with the development and progression of diabetic nephropathy; therapy reduces the development of microalbuminuria and retards the progression to overt proteinuria.[123]

Apart from reducing renal deterioration, treating hypertension positively influences cardiovascular risk as well as microvascular disease in persons with diabetes. The diabetic person has a 2- to 3-fold increased risk of a cardiovascular event; treatment of hypertension[124,125] reduces this risk by a greater extent than in persons without diabetes.

The level of blood pressure has a continuous relationship to progressive renal and adverse cardiovascular disease. It is believed that no "J" shaped relationship exists for this relationship. Intensive blood pressure control confers a relatively greater impact on cardiovascular risk reduction than tight glucose control.[86] Multiple antihypertensive agents may be needed to reach such blood pressure targets.

8.7 Use of antihypertensive agents

A In the absence of microalbuminuria or overt nephropathy, the principal intent is that of reducing the risk of a cardiovascular event. There is evidence for the initial antihypertensive agent to be from one of these classes: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers, diuretics, calcium channel blockers.

Grade A, Level Ib

A In the presence of microalbuminura, both ACE inhibitors and ARBs can be used.

Grade A, Level Ib

While blood pressure control is critical in preventing renal progression, ACE inhibitors and ARBs reduce microalbuminuria independent of their blood pressure lowering effects, hence conferring renoprotective effects independent of blood pressure control.[126-128]

A In the presence of overt nephropathy in type 1 diabetes, there is evidence that an ACE inhibitor can retard the progression of otherwise progressive renal disease.[126]

Grade A, Level Ib

A In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease.[127-129]

Grade A, Level Ib

If one class of drug is not tolerated, the other should be substituted. As ARBs cause less cough, they may be better tolerated. However, they are costlier. Combination therapy with ACE inhibitors and ARBs have, in small studies, been shown to reduce proteinuria and may provide better hypertension control.[130] ACE inhibitors are contraindicated in pregnancy and therefore should be used with caution in women of childbearing potential. There are no data on ARB use in pregnancy.

GPP The serum creatinine and potassium should be checked within 4 weeks of initiation of treatment with ACE inhibitors and ARBs to detect any untoward rise in the serum creatinine or hyperkalaemia.

GPP

GPP Progressive but non-continuous rise in the serum creatinine may be seen over 2 to 3 months after starting an ACE inhibitor or ARB. A short-term rise of less than 30% in the serum creatinine should not necessitate withdrawing the ACE inhibitor or ARB. Nevertheless, the possibility that there may be critical renal artery stenosis should be considered, especially in the presence of a renal artery bruit or refractory hypertension or asymmetric kidney sizes on ultrasound.

GPP

Some studies have demonstrated that the non-dihydropyridine calcium channel blockers can reduce the level of albuminuria, but no studies to date have demonstrated a reduction in the rate of fall of GFR with their use.[131] They may however be used as add-on therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs. Patients who do not tolerate ACE inhibitors or ARB may be treated with non-dihydropyridine calcium channel blockers.

GPP Therapy should aim to reduce albuminuria as much as possible, and it is reasonable to aim for a proteinuria target of less than 1 g/day or at least 50% of the pre treatment value.

GPP

8.8 Protein restriction

Low dietary protein intake may delay the progression of chronic renal failure in type 1 diabetic patients with overt nephropathy. It is not known if there is similar benefit in type 2 diabetic patients, or if a low protein diet in either group can delay the progression from microalbumin to overt nephropathy. At this point in time, the consensus is that type 1 diabetic patients with overt nephropathy should be maintained on a low protein diet of 0.8 g/kg/day.[132]

8.9 Lipid control

There is some evidence[133] that suggest optimizing lipids may be helpful in retarding progression of diabetic nephropathy. However, there is insufficient evidence at this point in time to make a firm recommendation on this.

GPP Referral to a Nephrologist

A referral is especially recommended when the following are present:

- Unexpected or rapid decline in renal function
- Difficulties with hyperkalaemia
- Atypical features, e.g. haematuria, absence of diabetic retinopathy, or casts in the urine sediment
- Presence of a renal bruit
- Difficult BP control
- Nephrotic range proteinuria (>3 g/day)

GPP

8.10 Summary of recommendations

C Screening for albuminuria should begin at 5 years after the diagnosis of type 1 diabetes; it should, however, begin immediately with the diagnosis of type 2 diabetes. Thereafter, screening for albuminuria should be done annually.

Grade C, Level IV

GPP Serum creatinine should be measured at least annually.

GPP

C The blood pressure target in all diabetic persons should be less than 130/80 mmHg. Diabetic patients with proteinuria levels exceeding 1 gram should try to have their BP lowered to less than 125/75 mmHg.

Grade C, Level IV

A In the absence of microalbuminuria or overt nephropathy, the principal intent is that of reducing the risk of a cardiovascular event. There is evidence for the initial antihypertensive agent to be from one of these classes: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers, diuretics, calcium channel blockers.

Grade A, Level Ib

A In the presence of microalbuminura, both ACE inhibitors and ARBs can be used.

Grade A, Level Ib

A In the presence of overt nephropathy in type 1 diabetes, there is evidence that an ACE inhibitor can retard the progression of otherwise progressive renal disease.

Grade A, Level Ib

A In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease.

Grade A, Level Ib

GPP The serum creatinine and potassium should be checked within 4 weeks of initiation of treatment to detect any rise in the serum creatinine or hyperkalaemia.

GPP

GPP Progressive but non-continuous rise in the serum creatinine may be seen over 2 to 3 months after starting on ACE inhibitor or ARB. A short-term rise of less than 30% in the serum creatinine should not necessitate withdrawing the ACE inhibitor or ARB. Nevertheless, the possibility that there may be critical renal artery stenosis should be considered, especially in the presence of a renal artery bruit or refractory hypertension or asymmetric kidney sizes on ultrasound.

GPP

GPP Therapy should aim to reduce albuminuria as much as possible, and it is reasonable to aim for a proteinuria target of less than 1 g/day or at least 50% of the pre treatment value.

GPP

GPP Type 1 diabetic patients with overt nephropathy should be maintained on a low protein diet of 0.8 g/kg/day.

GPP

GPP A nephrology referral is recommended when there are unexpected or rapid decline in renal function, difficulties with hyperkalaemia, atypical features e.g. haematuria, presence of casts in the urine sediment, presence of a renal bruit, difficult BP control, nephrotic range proteinuria (>3 g/day), and absence of retinopathy.

GPP

9 Prevention and Management of Eye Complications

9.1 Introduction

By 2010, the world diabetic population is expected to double to an estimated 221 million.[134] Currently, an estimated 2.5 million people worldwide are blind from diabetic retinopathy.[135] In Singapore, retinal conditions including diabetic retinopathy is a leading cause of blindness in adults.[136] In a major series of 13,296 diabetic patients examined by retinal photography in Singapore, 21.8% were found to have diabetic retinopathy, of which 10.8% were sight-threatening retinopathy.[137] Persons with diabetes are 25 times more likely to become blind compared to persons without diabetes.[138]

9.2 Screening and methodology

Screening for diabetic retinopathy via a single-field fundus photograph is not designed to be a substitute for a complete ocular examination. There is, however, good evidence that it can serve as a screening tool for the detection and evaluation of diabetic retinopathy.[139] The early detection of potentially sight-threatening diabetic retinopathy in often asymptomatic patients is the key to reducing blindness from diabetic retinopathy.

The primary healthcare practitioner has an important role in coordinating screening for diabetic retinopathy.

Direct ophthalmoscopy and retinal photography are the two common methods of screening available to primary healthcare practitioners. For better outcomes, fundal examination should be via dilated pupils unless there is a past history of acute glaucoma. Examinations through undilated pupils fail to detect proliferative retinopathy in about 50% of patients and macular lesions in all cases.[140]

Retinal photography is the more practical and preferred method as direct ophthalmoscopy is limited by the narrow field of view, is difficult to perform in the presence of poorly dilating pupils and/or cataracts,[141] and lacks a hard copy. Retinal photography for diabetic retinopathy achieves a sensitivity of 91.6%, with a specificity of 99.8% and is comparable to an ophthalmic examination in diagnosing diabetic retinopathy.[142]

9.3 Eye examination and minimum follow-up schedule

Table 10 Eye examination schedule[143,144]

Type of diabetes	Recommended time of first examination	Routine minimum follow-up
Type 1	Within 3-5 years after diagnosis of diabetes once patient is aged ten years or older	Yearly
Type 2	At diagnosis	Yearly
Pregnancy in pre-existing diabetes mellitus	Prior to conception and during early 1st trimester	As needed during pregnancy depending on results of first trimester examination

9.4 Systemic risk factors for progression of diabetic retinopathy

These include:
1. Duration of diabetes
2. Glycaemic control
3. Hypertension
4. Hyperlipidaemia
5. Microalbuminuria and proteinuria
6. Pregnancy
7. Anaemia
8. Smoking

The implications of these risk factors are summarised in Table 11 (page 82).

Duration of diabetes

The duration of diabetes is a predictor of the risk of diabetic retinopathy. In type I diabetics, retinopathy is uncommon at diagnosis but increases rapidly to 25% at 5 years, 75% at 10 years and 97.5% after 15 years of diabetes.[143] In type 2 diabetics, the figures vary from 28.8% (<5 years of diabetes) to 77.8% in those with 15 years or more of diabetes.[144]

Glycaemic control

The risk of development and progression of diabetic retinopathy can be reduced by optimising glycaemic control (without causing undue hypoglycaemia). Intensive therapy in type 2 diabetes (median HbA_{1c} 7.0%) reduces the overall incidence of microvascular complications (including diabetic retinopathy) by 25% compared to conventional treatment (median HbA_{1c} level 7.9%).[9]

A reduction in the mean HbA_{1c} by 0.9% (from 7.9 to 7.0%) translates into a corresponding reduction in the risk of microvascular complications (including retinopathy) by 37%.[145]

Similar results were reported in an Asian population.[79] In type I diabetic patients intensive glycaemic control reduces the risk of diabetic retinopathy by 50-75%.[10] Conversely, poor glycaemic control (HbA_{1c} > 10%) in type 1 diabetic patients increases the risk of developing retinopathy by eight times.[146] 53.2% of diabetics in the National Health Survey had poor blood glucose control with a mean HbA_{1c} of 8.5%.[147]

Rapid normalisation of blood glucose and progression of diabetic retinopathy

Intensive insulin therapy and rapid normalisation of blood glucose is associated with worsening of retinopathy in patients with long-standing poor glycaemic control. This is particularly so when the retinopathy is at or past the moderate non-proliferative (pre-proliferative) stage. Retinal assessment should be carried out before initiation of intensive insulin therapy and then at 3-monthly intervals for 6-12 months. In patients with more serious retinopathy (high-risk type), it may be prudent to delay the initiation of intensive treatment until laser photocoagulation is completed, especially if the HbA_{1c} is high.[148]

Hypertension

Hypertension is a known risk factor for progression of diabetic retinopathy. Over a median follow-up period of 8.4 years in type 2 diabetes, there is a 34% reduction in progression of retinopathy, and a 47% reduced risk of deterioration of the visual acuity by three lines in the tight blood pressure control group.[86] Microvascular end-points including retinopathy are decreased by 13% with each 10 mmHg reduction in the systolic blood pressure.[149]

Hyperlipidaemia

The prevalence of diabetic retinopathy is positively associated with increased cholesterol and triglyceride levels.[150] A higher likelihood of developing retinal hard exudations has been found in diabetic patients with increased serum cholesterol, low-density lipoprotein (LDL) cholesterol or triglyceride levels. This is associated with a higher risk of visual loss independent of the extent of macular oedema.[151]

There is a possibility that treatment of associated hyperlipidaemia may retard diabetic retinopathy.

Microalbuminuria and proteinuria

Increased urine albumin excretion was shown to be significantly associated with diabetic retinopathy ($P < 0.001$) in a type 2 diabetic population.[152] The presence of albuminuria should alert the physician to the presence of diabetic retinopathy. Both microalbuminuria and gross proteinuria are associated with increased risks of proliferative diabetic retinopathy in type 1 and 2 patients.[153] The relative risk of proliferative retinopathy developing in patients with gross proteinuria is 2.32 and 2.02 in type 1 and 2 diabetes, respectively.[154]

Pregnancy

Pregnancy in type I diabetes has been found to induce a transient increase in the risk of retinopathy. Increased surveillance is needed during the pregnancy and in the first year postpartum.[155]

Anaemia

Normocytic anaemia is associated with an increased risk of diabetic retinopathy, especially the severe form.[156] Concurrent treatment of anaemia may possibly slow the progression of diabetic retinopathy.[157]

Smoking

Evidence on the long term effects of smoking on the progression of diabetic retinopathy is not conclusive.[158,159] Smoking, however, is a significant risk factor for other diabetes-related complications especially for cardiovascular disease, and diabetics who smoke should still be encouraged to stop.

Table 11 Implications and management of systemic risk factors

Systemic risk factor	Risk factor modification	Anticipated effects
Hyperglycaemia	1% reduction in mean HbA_{1c}	37% reduction in risk of retinopathy[9]
Hypertension	10 mmHg reduction in blood pressure	13% reduction in risk of diabetic retinopathy[86]
Hyperlipidaemia	Treatment of hyperlipidaemia	Possible retardation of diabetic retinopathy
Microalbuminuria and proteinuria	To screen for retinopathy (especially for proliferative diabetic retinopathy)	No clear evidence that treatment of microalbuminuria and proteinuria has any impact on diabetic retinopathy
Pregnancy	To screen for retinopathy as in schedule.	Pregnancy is not a modifiable risk factor
Anaemia	Concurrent treatment of anaemia	Possible retardation of retinopathy

9.5 Classification of diabetic retinopathy

The International Clinical Diabetic Retinopathy Disease Severity Scale and Diabetic Macular Oedema Severity Scale[160] arose out of the need for a unified and global classification that would facilitate communication amongst diabetes care-givers (refer to Tables 12, 12A and 12B).

International Clinical Classification of Diabetic Retinopathy and Diabetic Macular Oedema Severity Scale

Table 12 Five levels of diabetic retinopathy

Disease severity level	Findings observable upon dilated ophthalmoscopy
No Apparent* Retinopathy	No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just microaneurysms but less than severe Non-Proliferative Diabetic Retinopathy
Severe Non-Proliferative Diabetic Retinopathy	Any of the following (4-2-1 rule): • More than 20 intraretinal haemorrhages in each of 4 quadrants • Definite venous beading in 2 or more quadrants • Prominent Intraretinal Microvascular Abnormalities (IRMA) in 1+ quadrant and no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or more of the following: • Neovascularisation • Vitreous/preretinal haemorrhage

* Diabetic retinopathy including macular oedema is difficult to diagnose with direct ophthalmoscopy alone.

Table 12A Diabetic macular oedema

Classification	Findings observable upon dilated ophthalmoscopy
Diabetic Macular Oedema Apparently* Absent	No retinal thickening or hard exudates in posterior pole
Diabetic Macular Oedema Apparently* Present	Some retinal thickening or hard exudates in posterior pole

Table 12B Diabetic macular oedema severity scale

Classification	Findings observable upon dilated ophthalmoscopy*
Diabetic Macular Oedema Present	• Mild Diabetic Macular Oedema Some retinal thickening or hard exudates in posterior pole but distant from the macula
	• Moderate Diabetic Macular Oedema Retinal thickening or hard exudates approaching the centre of the macula but not involving the centre
	• Severe Diabetic Macular Oedema Retinal thickening or hard exudates involving the centre of the macula

* Diabetic retinopathy including macular oedema is difficult to diagnose with direct ophthalmoscopy alone.

9.6 Referral for ophthalmologic opinion

1. Hard exudates/retinal thickening within one disc diameter of the fovea (diabetic macular oedema)
2. Severe non-proliferative diabetic retinopathy
3. Unexplained drop in visual acuity
4. Unexplained eye findings

Earlier referrals

1. Neovascularisation from proliferative diabetic retinopathy
2. Pre-retinal and/or vitreous haemorrhage
3. Rubeosis iridis (new vessels on the iris)

Urgent referrals

1. Sudden loss of vision
2. Retinal detachment
3. Neovascular glaucoma

9.7 Treatment

Aspirin

Aspirin has not been found to reduce the risk of visual loss or prevent the development of diabetic retinopathy. The risk of vitreous haemorrhage is not increased with the use of aspirin. It is not contraindicated for use in patients requiring it for cardiovascular disease or other medical indications.[161]

Antioxidants, aldose reductase inhibitors and other agents

No protective effect on diabetic retinopathy has been found with the use of antioxidants.[162] The routine use of aldose reductase inhibitors, growth hormone suppression, angiotension-converting enzyme (ACE) inhibitors for the sole purpose of reducing the progression of diabetic retinopathy is also not supported by available evidence.

Argon laser photocoagulation

Laser photocoagulation is the mainstay of treatment for diabetic retinopathy. However, vision already impaired by diabetic retinopathy, in particular, by macula involvement cannot be usually restored by laser therapy. Laser photocoagulation is aimed at reducing further damage from macula involvement and to reduce the risk of complications from the retinal neovascularisation. Early detection of diabetic retinopathy is crucial.

Laser photocoagulation has been found to reduce the rate of severe visual loss by 50% in type 2 diabetics with severe non-proliferative (pre-proliferative) and proliferative retinopathy.[163] Laser treatment (focal/grid) for diabetic macular oedema (maculopathy) is also effective with a similar reduction in visual loss rate (50%).[164]

Vitreous surgery/vitrectomy

Vitreous surgery (vitrectomy) is sometimes indicated in patients with advanced proliferative diabetic retinopathy. Vitreous haemorrhage and/or eyes with traction detachment involving the macula are the main indications. In particular, early vitrectomy has also been shown to be beneficial in type 1 patients with dense vitreous haemorrhage.[165]

The stages of diabetic retinopathy and the management are illustrated in Annex 1 (page 151).

Table 13 Management and stage of diabetic retinopathy

Stage/ Severity	Relative Risk of Progression	General Management	Eye Examination Frequency	Laser Treatment
No retinopathy		Optimisation of blood glucose, blood pressure and lipids	12 monthly	No
Mild Non-Proliferative Diabetic Retinopathy		Optimisation of blood glucose, blood pressure and lipids	6-12 monthly	No
Moderate Non-Proliferative Diabetic Retinopathy	Early Proliferative Diabetic Retinopathy in 1 year: 5.4 -11.9% High risk Proliferative Diabetic Retinopathy in 1 year: 1.2-3.6%	Optimisation of blood glucose, blood pressure and lipids	3-6 monthly	Occasionally, if not compliant with close follow-up, for impending cataract operation, or pregnancy and considerations of the state of the fellow eye.
Severe Non-Proliferative Diabetic Retinopathy	Early Proliferative Diabetic Retinopathy in 1 year. 50.2% High Risk Proliferative Diabetic Retinopathy in 1 year: 14.6-45.0%	Manage systemic risk factors Rapid normalisation of blood glucose prior to laser has increased risks		Pan-retinal photocoagulation.

Stage/ Severity	Relative Risk of Progression	General Management	Eye Examination Frequency	Laser Treatment
Proliferative Diabetic Retinopathy		Manage systemic risk factors Rapid normalisation of blood glucose prior to laser has increased risks		Pan-retinal photocoagulation.
Vitreous / Preretinal Haemorrhage Neovascular Glaucoma		Manage systemic risk factors Rapid normalisation of blood glucose prior to laser has increased risks		Pan-retinal photocoagulation (if clear media allow) Lower Intraocular Pressure by medical means Consider various non-surgical / surgical options, where appropriate
Diabetic Macula Oedema		Manage systemic risks factors Rapid normalisation of blood glucose prior to laser has increased risks	3-4 monthly (Mild macular oedema)	Laser treatment (focal/grid) for moderate and severe diabetic macular oedema

Note:
Adapted and based on the American Academy of Ophthalmology, Preferred Practice Patterns. Diabetic Retinopathy 2003. The above treatment plan and strategy is meant as a general guide only. Specific treatment will depend on various clinical considerations and should be individualised.

9.8 Other ocular manifestations of diabetes mellitus

1. Corneal abnormalities (increased corneal abrasion and decreased corneal sensation)
2. Cataract
3. Optic neuropathies (acute ischemic optic neuropathy, diabetic papillopathy)
4. Cranial neuropathies (third, fourth and sixth cranial neuropathies)
5. Glaucoma
6. Orbital fungal infection (mucormycosis)

9.9 Summary of recommendations

Screening

C All patients diagnosed with diabetes require regular visual acuity assessment and eye examinations by trained personnel to screen for diabetic retinopathy using a test of adequate sensitivity.

Grade C, Level IV

C Type 1 diabetic patients should be examined 3-5 years after diagnosis of diabetes, and at least once yearly subsequently. Type 2 diabetic patients should have an ocular assessment at the time of diagnosis and at least once yearly subsequently.

Grade C, Level IV

C Retinal screening preferably using retinal photography, or direct ophthalmoscopy (if retinal photography is not available) through dilated pupils is recommended.

Grade C, Level IV

Management of systemic risk factors

A Good glycaemic control (HbA_{1c} preferably 6.5 to 7.5%) should be instituted to reduce the risk of retinopathy.

Grade A, Level Ib

A Good control of blood pressure at or below 130/80 mmHg should be instituted to reduce the progression of diabetic retinopathy.

Grade A, Level Ib

C Significant hyperlipidaemia should be treated to retard diabetic retinopathy.

Grade C, Level IV

Referrals

GPP Diabetic patients found to have diabetic retinopathy by their physicians should be referred for further ophthalmological assessment.

GPP

A Timely laser therapy should be offered to patients with proliferative diabetic retinopathy and diabetic macular oedema. Panretinal and focal/grid laser treatment results in at least a 50% reduction in the risk of visual loss.

Grade A, Level Ib

Treatment

A Laser photocoagulation should be instituted for severe and proliferative retinopathy as it produces a 50% reduction in risk for severe visual loss and need for vitrectomy.

Grade A, Level Ib

10 Prevention of Diabetic Foot Complications

10.1 Introduction

Foot ulcers and amputations are a major cause of morbidity and mortality in people with diabetes.[166] In Singapore, approximately 700 lower extremity amputations (LEA) are performed in diabetic patients annually.[167] Foot complications affect not only the individual but also the country in terms of productivity and costs. The estimated costs of an LEA in the USA is US$12,230 to US$40,563[168] (per individual) and US$709,000,000[169] for the country (annually).

10.2 Screening

Studies show that a systematic screening, treatment and patient education protocol can reduce the lower extremity amputation rate by 44-85%.[170,171] Risk identification is fundamental for effective preventive management of the foot in people with diabetes.[166]

10.3 Risk identification

The following foot-related risk conditions are associated with an increased risk of amputation (see Table 14, page 91).

Table 14 Diabetic foot-related risk conditions

Description	Signs & Symptoms
Ulceration or prior lower extremity amputation	• History of ulceration • History of Lower extremity amputation
Peripheral neuropathy	• Negative monofilament* sensation • Negative pin prick sensation • Negative tuning fork 128Hz (vibratory perception threshold) sensation • Presence of paraesthesia or anaesthesia
Peripheral vascular disease	• Absent pedal pulses • Absence of hair • Absence of gradual temperature gradient • Intermittent claudication/rest pain
Altered biomechanics	• Bony deformity • Gross foot deformity • Limited joint mobility • Osteoarthropathy (Charcot joint) • Abnormal gait
Dermatological & nail pathologies	• Presence of ulceration (with/without infection) • Callus with haemorrhage • Ingrown toenails, mycotic toenails, onychogryphotic nails • Evidence of neglect or poor foot hygiene • Interdigital maceration • Fissuring (especially heels) • Skin and/or tinea pedis infections
Poor Footwear	• Slippers, “flip-flops”, “thongs” • Tight or ill-fitting shoes • Abnormal wear patterns

* Semmes-Weinstein 5.07 monofilament

People with one or more high-risk foot conditions should be evaluated more frequently for the development of additional risk factors.[166] For those at high risk of foot pathology, a referral to the community or hospital specialist footcare team should be considered.[172]

10.4 Footcare protocol

Table 15 Footcare protocol

Risk	Treatment provided by	Treatment modalities	Review
At Risk	Primary medical practitioner and nursing staff trained in diabetic foot care	• Screening of foot • DM footcare education/footwear advice	• Annually • Frequent reinforcement
High Risk	Specialised footcare team: podiatrists, diabetes specialist, orthopaedic surgeon, vascular surgeon, diabetes nurse educator	• Wound debridement and management • Custom made orthosis/insoles for pressure redistribution • Footwear adaptations • DM footcare education/footwear advice	• Regular interval as clinically indicated • Frequent reinforcement

10.5 Prevention of high risk conditions

The aim of management is to keep the foot from developing high risk conditions. The following components of multidisciplinary management are important.

a) Mechanical control
b) Metabolic control
c) Education

10.5.1 Mechanical control

Mechanical control involves wearing the correct footwear (refer to Table 17, page 96) and the diagnosis and treatment of common foot problems.

10.5.2 Metabolic control

Optimization of glycaemic control is important. Smoking cessation should be encouraged to reduce the risk of vascular disease complications.

10.5.3 Education

All patients, regardless of risk category, require ongoing foot health education provided by a health professional trained in diabetic foot care.[172] Lack of education on footcare has been associated with a 3-fold increased risk of amputations. Specific footcare and footwear education can be performed by a doctor, podiatrist or diabetes nurse educator. Being well informed and motivated is the best defense against diabetic limb loss.[173]

Foot health education should cover the following areas:

- Explanation of basic concepts of vascular disease, neuropathy, increased liability to infection and its relevance to the progression of foot complications
- Basic wound dressing concepts for superficial wounds
- Need for daily foot inspection
- Recognition of problems, deterioration of wounds and when to seek professional medical help
- Foot hygiene
- Suitable footwear
- Avoidance of trauma
- The need to change specific social habits e.g. stop smoking, eat a healthy diet and exercise regularly
- The need to maintain optimal glycaemic control

10.6 Summary of recommendations

B All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions.[166]

Grade B, Level IIb

B The assessment of the feet involves risk identification, treatment and patient education appropriate to the level of risk.[170,171]

Grade B, Level IIa

A All patients, regardless of risk category, should receive ongoing education on footcare and footwear advice.[172]

Grade A, Level lb

B Patients identified with foot-related risk conditions should have access to a specialized footcare team which should include diabetes specialist, podiatrist, physiotherapist trained in diabetes, diabetes nurse educator and vascular and orthopaedic surgeon.[172]

Grade B, Level III

A Urgent referral to a specialized footcare team is needed in the presence of ulcerations, severe foot infection and gangrene.[172]

Grade A, Level Ib

Table 16 Practical footcare guidelines

DO's	DON'Ts
Inspect Your Feet Everyday ✓ **Do** look on top, underneath, in between toes, around heels. ✓ **Do** look for cuts, scratches, abrasions or any broken skin ✓ If found, **Do** wash with saline, dress with dry sterile daily dressing. ✓ If wound doesn't start to heal within 2 days, **Do** consult your doctor or podiatrist. **Foot Hygiene** ✓ **Do** wash feet daily using mild soap and warm water. Pay attention to in between toes. ✓ **Do** test water temperature with wrist or arm first to ensure not too hot. ✓ **Do** pat dry especially in between toes. ✓ If feet are dry, **Do** use moisturizing cream nightly except in between toes. **Socks / Hosiery** ✓ **Do** ensure socks/stockings are not too tight. ✓ **Do** change socks/stockings daily. ✓ **Do** ensure proper fit i.e. no bunching or wrinkling underneath. **General Hints** ✓ **Do** cut toenails straight across and not too short. ✓ **Do** seek help from your doctor, podiatrist or nurse educator if you are unsure of anything on your feet. ✓ **Do** exercise. ✓ **Do** maintain good diabetes control.	**Foot Neglect** ✗ **Don't** neglect your foot as small problems can turn into big problems quickly. **Bathroom Surgery** ✗ **Don't** cut hard skin, ingrown toenails yourself. ✗ **Don't** use corn plasters, corn cures. **General Hints** ✗ **Don't** smoke ✗ **Don't** walk barefoot. Always wear footwear inside and outside the house.

Table 17 Practical footwear guidelines

DO's	DON'Ts
Fitting ✓ **Do** ensure a good fit. One thumbnail width from the end of the longest toe to the end of the shoe. ✓ **Do** wear shoes which are comfortable. **Style** ✓ **Do** wear closed-in shoes for protection. Sports shoes are ideal. However, sports sandals are acceptable. Remember to check your feet regularly. ✓ **Do** wear shoes with a rounded toebox. ✓ **Do** wear shoes with laces or straps or buckles. **General Hints** ✓ **Do** check inside shoes for foreign objects, sharp seams, torn linings before you put them on. ✓ **Do** "wear in" new shoes gradually e.g. 1 hour the 1st day, 2 hours the 2nd day, 3 hours the 3rd day until you can wear them through the day. Check feet for signs of rubbing – redness, blisters, pressure areas, open wounds. ✓ **Do** alternate between 2 pairs of shoes i.e. use one pair for Mon, Wed, Fri, Sun and the other pair for Tues, Thurs, Sat. ✓ **Do** clean and wash shoes regularly.	**Fitting** ✕ **Don't** wear too tight or too loose shoes ✕ **Don't** wear shoes which are required to *stretch* for a good fit. **Style** ✕ **Don't** wear slippers, flip-flops, thongs. ✕ **Don't** wear shoes with pointy toes. ✕ **Don't** wear shoes with high heels. The recommended height is 1 inch with a broad base. **General Hints** ✕ **Don't** sacrifice comfort and protection for the sake of fashion.

11 Management of Women with Pregestational and Gestational Diabetes Mellitus

11.1 Introduction

Diabetes mellitus in pregnancy may have acute as well as long-term complications for mother and foetus. In order to reduce the incidence of such complications, good metabolic control prior to and during pregnancy is important.[174,175]

With an increasing number of older women going on to have children, gestational diabetes has become increasingly important. The prevalence is 1-14% of all pregnancies depending on the population studied and the diagnostic tests employed.[176] In Singapore, approximately 8.6% of all pregnancies are complicated by gestational diabetes.[177]

11.2 Definition

Diabetes mellitus in pregnancy falls into 2 categories:

Gestational diabetes (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether or not the condition persists after pregnancy.[178-181] It does not exclude the possibility that unrecognised glucose intolerance may have been present before the onset of the index pregnancy. Women who are found to have fasting hyperglycaemia or abnormal carbohydrate intolerance in the first trimester may have preexisting diabetes and should be treated in the same fashion as women who are known to have glucose intolerance before pregnancy. In the majority of cases of GDM, glucose regulation will return to normal after delivery.[178-181]

Pregestational diabetes is diagnosed when the woman has diabetes before the onset of pregnancy. Diabetic women in the reproductive age group, especially if they intend to have children, should receive pre-pregnancy counselling.[174,182,183]

11.3 Pre-pregnancy counselling

All diabetic women in the reproductive age group should receive pre-pregnancy counselling.[174,182,183] This should be performed jointly by a multi-disciplinary team skilled in diabetic care, including the physician, obstetrician, dieticians, nurse-educators and other specialists. Its aims are:

- to provide education and counselling about the risk of malformation associated with unplanned pregnancy and poor metabolic control
- to assess suitability for pregnancy
- to look for complications of diabetes, and to evaluate and treat these complications prior to the onset of pregnancy
- to adjust and convert drugs like oral hypoglycaemics, some antihypertensives, and other treatments used pre-pregnancy to alternatives which are safer during pregnancy
- to provide information about the use of effective contraception, unless the patient is in good metabolic control and actually trying to conceive
- to achieve optimal control prior to and during very early pregnancy
- to provide information about what to expect in pregnancy and general measures to improve outcome.
- to provide an opportunity for pre-pregnancy dietary advice and folate supplements

11.4 Screening for and detection of gestational diabetes

Deterioration of glucose tolerance occurs during pregnancy, particularly in the third trimester. There is lack of uniformity in the approach to screening and diagnosis of GDM internationally. This has hampered resolution of the considerable controversy about the clinical importance of GDM and the magnitude of its impact on mother and offspring. Until better consensus is reached, the following guidelines are subject to review and changes when more data is available.

Screening

Risk assessment for GDM should be undertaken at the first antenatal visit. Women are at high risk for GDM if they have:

- marked obesity,
- a strong family history of type 2 diabetes,
- a personal history of previous GDM or large babies >4 kg,
- previous poor obstetric outcomes usually associated with diabetes.

Women at *high risk* for GDM should be evaluated for glucose intolerance with an oral glucose tolerance test (OGTT) as early in pregnancy as feasible.[31,178-180,184] Re-evaluation may be necessary at 28 weeks if glucose intolerance is not present at the early screen.

Those at *low risk* for the development of glucose intolerance during pregnancy include women who have no previous history of abnormal glucose tolerance or previous poor obstetric outcomes usually associated with diabetes, AND who have ALL the following characteristics:

- age <25 years,
- normal body weight, and
- no family history of diabetes.

It is unlikely to be cost-effective to screen such patients with routine OGTT.[31,178,179]

For those at *low risk*, urine for glucose should be obtained at each antenatal visit. If urine glucose is 1+ or more, random blood glucose levels should be ascertained. OGTT is necessary if the random venous plasma glucose >6.6 mmol/l more than 2 hours after a meal, or >7.0 mmol/l within 2 hours of a meal.[185]

Diagnosis

GDM is diagnosed with a 75 g OGTT. A fasting venous plasma value ≥7.0 mmol/dl (126 mg/dl) or a 2-hour venous plasma value of ≥7.8 mmol/dl (140 mg/dl) is diagnostic of GDM.[186] Casual venous plasma levels ≥11.1 mmol/l (200 mg/dl) on 2 successive occasions would confirm GDM without recourse to OGTT.

11.5 Antenatal management of diabetes in pregnancy: gestational and pregestational diabetes

Close surveillance of mother and foetus must be maintained in all instances of diabetes in pregnancy. All women with pregestational DM or diagnosed with GDM should receive specialized care.[185]

Metabolic management

In GDM, *dietary control* should be used in the first instance to attain glycaemic goals without excessive ketonaemia and ketonuria.[180,185-187] Sweet foods should be avoided and caloric intake reduced if the woman is overweight. The diet should contain more complex carbohydrates, more fibre and less saturated fat. Nutritional counselling should be individualized to take into account the patient's body habitus, weight gain and physical activity.

If nutritional therapy does not consistently maintain a fasting or preprandial capillary glucose of <5.5 mmol/l and/or a 2-hour postprandial capillary glucose of <6.7 mmol/l on two or more occasions within a 1-2 week interval, insulin therapy should be considered.[178,179] This is particularly in association with evidence of a macrosomic foetus.

Human insulin should be used when insulin is prescribed.[178-180] Insulin administration should be individualized to achieve glycaemic goals stated previously. Sometimes a multi-dose regimen of insulin administration is needed. In women with established DM, intensive insulin therapy is often necessary to maintain near-normal glucose control.[188]

The tight control of blood sugar levels is necessary to reduce complications of pregnancy and reduce perinatal mortality and morbidity for the infant. However, there is no clear evidence of benefit from very tight glycaemic control, with its attendant episodes of maternal hypoglycaemia and substantial impact on lifestyle with over tight control.[189] The management strategy should be to maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l (<100 mg/dl) in the fasting state, and/or <7.8 mmol/l (<140 mg/dl) at 1 hour, and/or <6.7 mmol/l (<120 mg/dl) 2 hours post-prandial.[176,177,185]

Daily self-monitoring of blood glucose appears to be superior to intermittent office monitoring of plasma glucose.[178] Postprandial testing may be associated with better outcomes than preprandial testing in women with gestational diabetes requiring insulin treatment.[190] Urine glucose monitoring is not useful for monitoring diabetes in pregnancy.[179]

Women with active lifestyles should be encouraged to continue on a programme of moderate exercise.[179,180,191] Recently, studies providing evidence for oral hypoglycaemic agents in pregnancy have been published.[192] However, until more randomised controlled trials are performed, oral hypoglycaemic agents are not recommended during pregnancy[178,179] under normal circumstances.

Foetal surveillance

Decisions about foetal surveillance should be based on the severity of maternal hyperglycaemia and the presence of other adverse clinical factors, i.e. past poor obstetric history or coincident obstetric complications like hypertension and intrauterine growth retardation. The clinical utility of routine tests of foetal surveillance in an uncomplicated gestational diabetic pregnancy has not been established.[193] There is no single reliable test for assessment of foetal well being in diabetic pregnancies. The underlying pathophysiology of the diabetic pregnancy is poorly understood and likely to be multifactorial, but foetal monitoring methods that are applied in other high risk pregnancies have been used.[194] The assurance offered by different biophysical monitoring modalities for metabolically based foetal compromise is probably of short duration.[185,194]

Mothers should be taught to monitor fetal movements during the last 10-12 weeks of pregnancy and to report immediately any reduction in the perception of foetal movements.[31,178,195]

An ultrasound examination should be performed at between 18-22 weeks for congenital anomalies in pregestational diabetic women and when GDM is diagnosed in the first trimester.[183] Ultrasound examination to measure growth (especially foetal abdominal circumference) and liquor volume at 29-33 weeks gestation may be useful.

Non-stress testing with cardiotocography and umbilical Doppler flow studies may be considered in cases where hyperglycaemia warrants insulin therapy and in cases where other high-risk factors are present.[196]

Maternal surveillance

The measurement of blood pressure, body weight and urinary protein is recommended at each antenatal visit to detect development of pregnancy-induced hypertension.[178,185,197]

In women with pregestational diabetes, serum creatinine, uric acid and electrolytes should be assessed at the initial visit and in the third trimester. They should also be referred to the ophthalmologist for screening.[178,185,198]

Route and timing of delivery

The timing of delivery should be determined by a combination of maternal and foetal risk factors. If a patient has maintained good glycaemic control and all parameters of foetal surveillance are normal, she may await spontaneous onset of labour.[199]

Data are not available to indicate whether or not there is greater perinatal mortality/morbidity in the infants of women with well-controlled GDM if pregnancy is allowed to continue past 40 weeks gestation. It would be reasonable to intensify foetal surveillance when pregnancy is allowed to continue beyond 40 weeks gestation.[180,185]

Intrapartum management

The presence of diabetes should not itself constitute an indication for elective caesarean delivery. However, cephalo-pelvic disproportion and shoulder dystocia accompanied by traumatic birth injury are more likely with vaginal delivery of large infants of diabetic women.[178] The aim is spontaneous vaginal delivery, but this may not always be possible.

Capillary blood glucose levels should be determined at 1-4 hour intervals from onset of labour. Insulin may be required if maternal blood glucose exceeds a target range of 70-120 mg/dl (3.9-6.6 mmol/l).[178,180,185]

Electronic foetal monitoring should be used routinely in all diabetic pregnancies.

11.6 Management of the Infant of a Diabetic Mother

The neonatologist should be informed of deliveries of infants of diabetic mothers so that possible complications like hypoglycaemia may be monitored and treated early. Screening for abnormalities should also be performed soon after birth.[180] Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life. Infants of diabetic mothers should be fed early.[200]

11.7 Postnatal Management

Breastfeeding is not contraindicated in women with diabetes. Until lactation is established, formula feeds may be necessary to prevent neonatal hypoglycaemia.

Because of limited clinical data regarding the exposure of oral hypoglycaemic drugs to the infant via breast milk, and the potentially serious effects of neonatal hypoglycaemia, breastfeeding is not recommended while the mother is on oral hypoglycaemic drugs.[201]

Women with GDM rarely require insulin after delivery. In women with pre-pregnancy diabetes, the insulin dose should be reduced to pre-pregnancy levels.

Women with GDM are at increased risk for developing diabetes subsequently.[202,203] An OGTT should be performed at least 6 weeks postpartum and the patient reclassified according to criteria accepted in the non-pregnant state.[31,179,180] Patients should be instructed in lifestyle modification aimed at reducing weight and increasing physical activity in the expectation that this will reduce the risk of subsequent diabetes.

All subsequent pregnancies carry a risk for GDM. Early evaluation of glucose tolerance in future pregnancies should be stressed. Regular re-evaluation of glucose tolerance should be considered, even in the absence of symptoms of diabetes.[204]

11.8 Contraception

Contraception should be discussed with all women of childbearing age. Low dose oestrogen-progestin oral contraceptives[179,185] and the intra-uterine contraceptive devices (IUCD)[185] are not contraindicated in women with previous gestational diabetes.

In women with impaired or abnormal glucose tolerance, glucose and lipid profiles should be monitored if low-dose oestrogen-progestin oral contraceptives are used. These should, however, be avoided in women with complications of diabetes and those at risk for vascular disease.[205] There is concern about the risk of infection with IUCD use. Women with diabetes are particularly susceptible to bacterial infection.

Sterilisation is the method of choice when the family is complete.

11.9 Summary of recommendations

Preconception care

B All diabetic women in the reproductive age group should receive pre-pregnancy counselling, particularly before starting a family.

Grade B, Level IIa

Screening and diagnosis

B Women at high-risk for gestational diabetes (GDM) should undergo an OGTT as early in pregnancy as feasible. Re-evaluation may be necessary at 28 weeks if glucose intolerance is not present at the early screen.

Grade B, Level IIa

B In all other patients, urine for glucose should be obtained at each antenatal visit and random blood sugar levels ascertained when there is ≥1+ glycosuria. A diagnostic test is necessary if the random plasma blood glucose >6.6 mmol/l more than 2 hours after a meal, or >7.0 mmol/l within 2 hours of a meal.

Grade B, Level III

Antenatal care

B In gestational diabetes (GDM), dietary control should be used in the first instance to attain glycaemic goals. If nutritional therapy does not consistently maintain a fasting or pre-meal capillary blood glucose of <5.5 mmol/l and/or a 2-hour postprandial capillary blood glucose of <6.7 mmol/l on two or more occasions within a 1-2 week interval, insulin therapy should be considered.

Grade B, Level IIa

B In established diabetics (pregestational diabetes), intensive insulin treatment is often necessary to maintain target blood glucose levels.

Grade B, Level IIb

B Maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting or premeal state, and/or <7.8 mmol/l 1 hour after meals, and/or <6.7 mmol/l 2 hours after meals.

Grade B, Level III

B All women diagnosed with GDM and pregestational DM should receive specialized care.

Grade B, Level III

Infants of diabetic mothers

B Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life. Infants of diabetic mothers should be fed early.

Grade B, Level III

Postnatal management

B Breastfeeding is not contraindicated in women with diabetes.

Grade B, Level III

B An OGTT should be performed at least 6 weeks postpartum and the patient reclassified and counselled according to criteria accepted in the non-pregnant state.

Grade B, Level IIb

Contraception

B Low dose oestrogen-progestin oral contraceptives and the intra-uterine contraceptive devices are not contraindicated in women with previous GDM.

Grade B, Level III

B Oestrogen-progestogen contraceptives should be avoided in women with complications of diabetes and those at risk of vascular disease.

Grade B, Level III

12 Management of the Child and Adolescent with Diabetes Mellitus

12.1 Introduction

The incidence of childhood type 1 diabetes mellitus in Singapore is 2.46 per 100,000 children aged 1-12 years.[206] However, with the recent global epidemic of obesity in children and adolescents, there is an increase in the incidence of type 2 diabetes reported in children from the United States, United Kingdom, Australia and New Zealand.[207,208] The emergence of type 2 diabetes mellitus in childhood and adolescence has also been reported in Asian countries, with the representative proportions of 21% in Japan, 18% in Thailand, 14% in Malaysia, and 10% in Singapore.[209,210]

12.2 Treatment

The care of diabetes in childhood and adolescence, whether type 1 or type 2, is best accomplished by a multi-disciplinary team in an institutional setting,[211,212] with a programme of ongoing diabetes education. Diabetes education is the foundation of good diabetes control.[213] This includes teaching the parent and child about blood glucose monitoring, administering insulin injections, recognizing and treating hypoglycaemia and managing sick days.[214] As the child grows and matures, age-appropriate diabetes education should be imparted, with emphasis on self-care responsibilities shifting from parent to patient.

In adolescents with diabetes, attempts to foster independence should be encouraged. The transition to adult diabetes services should be carefully managed, as adolescents are vulnerable to being lost to follow-up.[215]

12.3 Goals of treatment

The goals of treatment for childhood and adolescent diabetes include:[211,216]

a. Normal physical growth and pubertal development.

b. Normal psychosocial development and full participation in age-appropriate activities.

c. Good glycaemic control with minimal hypoglycaemia.

d. Absence of diabetic ketoacidosis.

e. Minimization and early detection and treatment of complications.

12.4 Targets of glycaemic control

Age-appropriate targets for glycaemic control in children should take into account the dangers of hypoglycaemia,[217,218] and the proven benefits of intensive therapy, and are tabulated in Table 18 below:[218]

Table 18 Targets of glycaemic control

Age group	Target pre-meal blood glucose levels	HbA_{1c}
<6 years	5-12 mmol/l	7-9%
6-12 years	4-10 mmol/l	6-8%
>13 years	4-8 mmol/l	6-8%

The optimal postprandial blood glucose level ranges from 5.0-11.0 mmol/l, with the ideal nocturnal blood glucose level ranging from 3.6-6.0 mmol/l. If the fasting blood glucose level is <4 mmol/l, the possibility of antecedent nocturnal hypoglycaemia should be considered.[213]

Screening for diabetic complications should begin in childhood. Regular screening and treatment should be initiated for hypertension, hyperlipidaemia, microalbuminuria, diabetic retinopathy and autoimmune thyroid disease.[218-221]

A. Type 1 diabetes mellitus

Improved glucose control within defined glucose and HbA_{1c} targets (as tabulated above), while avoiding hypoglycaemia, is the treatment goal for all children and adolescents with type 1 diabetes.[218] Type 1 diabetes mellitus in children and adolescents should be managed by an endocrinologist.

Rapid acting insulin analogues

In prepubertal children, the rapid acting insulin analogues (insulin lispro and aspart), administered as pre-prandial bolus injections closer to mealtime than regular insulin, can significantly lower postprandial glucose levels compared with regular insulin.[222,223] For young children whose diet may vary, post-prandial administration of a rapid acting insulin analogue is as effective and safe as the traditional treatment with pre-prandial regular insulin.[224]

Long acting insulin analogues

Glargine, which has no pronounced plasma peaks, has the advantage of once-daily administration, with the potential of reducing the risk of nocturnal hypoglycaemia. In the limited trials for children and adolescents, glargine has been shown to improve the fasting blood glucose levels compared to NPH insulin, although there was no significant difference in baseline to end-point HbA_{1c} levels, or in the percentage of symptomatic hypoglycaemia events.[225,226] However, glargine, when used in addition to lispro and NPH, resulted in a significant reduction in hypoglycemic events, a reduction in the HbA_{1c} levels and a reduction in the daily insulin dose.[227] There are inadequate data on the safety and efficacy of glargine in pre-school children.

B. Type 2 diabetes mellitus

Screening for type 2 diabetes in children and adolescents

Screening for diabetes and disorders of glucose tolerance should be considered for children who are overweight,* with the following risk factors:[228]

a. Family history of type 2 diabetes in first and second degree relatives and/or
b. Presence of acanthosis nigricans, or conditions associated with insulin resistance (hypertension, dyslipidaemia, polycystic ovarian syndrome)

* Overweight is currently defined by weight >120% of ideal [50th percentile] weight for height. However, the BMI centile corresponding to 25.0 kg/m^2, based on the WHO BMI cut-offs for Asians who are overweight, may eventually be used. These BMI cut-offs points are currently being reviewed.

Testing in these individuals should be done at least every 2 years starting from age 10 years or at the onset of puberty, if the latter occurs at a younger age.[228] The fasting plasma glucose (FPG) and 2-hour oral glucose tolerance test (OGTT) are both acceptably sensitive and specific.[228] However, the FPG is preferred because of its lower cost and greater convenience.

Treatment of children and adolescents with type 2 diabetes mellitus

The presentation of children and adolescents with type 2 diabetes mellitus can range from asymptomatic hyperglycaemia to diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar nonketotic (HHNK) states. Early consultation and referral to the endocrinologist should be considered, especially with the acute emergencies.[228]

The less ill child with type 2 diabetes may be treated initially with diet and exercise, unless symptomatic or severely hyperglycaemic. Clinical features that warrant initial treatment with insulin include dehydration, presence of ketosis and acidosis.[228] With time, metabolic control may change, necessitating the re-evaluation of treatment, such as tapering of insulin and the introduction of an oral agent.

Insulin and metformin (for children above 10 years) are the only drugs approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes in children. Oral hypoglycaemic agents have potentially greater compliance and convenience for the patient and family. Insulin should be started if oral agents fail to attain target control.

Metformin is the first oral agent recommended in children and adolescents with type 2 diabetes mellitus. It does not predispose to hypoglycaemia, body weight often remains stable with metformin, and it is relatively safe and effective.[228,229] However, because of the concerns of lactic acidosis, metformin is contraindicated in children with impaired renal function and hepatic disease, and should be discontinued with any acute illness associated with dehydration or hypoxaemia.

If monotherapy with metformin is not successful over 3-6 months, several alternatives can be considered. These include the use of a sulfonylurea, insulin or an insulin secretagogue (meglitinide).[228] However, the routine

use of the thiazolidenediones in children and adolescents cannot be recommended until safety information is available.

Children with impaired glucose tolerance and obesity should be counselled about the risks of diabetes, and managed with dietary modification and exercise.[230,231] It has not been established whether metformin can reduce the risk of type 2 diabetes mellitus in these children.[232]

The efficacy and safety of long term treatment of children with statins has not been extensively studied. In general, bile-acid sequestrants are the preferred anti-hyperlipidemic drugs in children and adolescents.[232] An angiotensin-converting enzyme inhibitor may be considered for use in children and adolescents with hypertension and diabetes, although its use has not been widely studied.

12.5 Summary of recommendations

B In childhood type 1 diabetes mellitus, the aims of treatment are:

a. Normal physical growth and pubertal development.
b. Normal psychosocial development and full participation in age-appropriate activities.
c. Good glycaemic control with minimal hypoglycaemia.
d. Absence of diabetic ketoacidosis.
e. Minimization and early detection and treatment of complications.

Grade B, Level IIa

B The care of diabetes in childhood and adolescence, whether type 1 or type 2, is best accomplished by a multi-disciplinary team in an institutional setting.

Grade B, Level IIa

B Screening for diabetes should be considered for children and adolescents who are overweight, have a strong family history of diabetes and have acanthosis nigricans, hypertension, dyslipidaemia or the polycystic ovarian syndrome. Testing in these individuals should be done at least every 2 years starting from age 10 years or at the onset of puberty, if the latter occurs at a younger age.

Grade B, Level IIa

C Children and adolescents with impaired glucose tolerance and obesity should be managed with diet and exercise.

Grade C, Level IV

C Children with type 2 diabetes mellitus may initially be treated with lifestyle modifications (diet and exercise), unless they are symptomatic or severely hyperglycaemic.

Grade C, Level IV

C Oral hypoglycaemic agents may be started in children with type 2 diabetes if glycaemic targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control.

Grade C, Level IV

13 Prevention of Type 2 Diabetes

In the last decade, several studies have examined the feasibility and benefit of various strategies to prevent or delay type 2 diabetes.

At least five conditions should be met to justify instituting a programme to prevent a disease. Ideally, these conditions should be applied to the prevention of diabetes-related morbidity and mortality rather than merely the diagnosis of diabetes.

First, the disease to be prevented should be an important health problem. Diabetes, without question, fulfils this criterion. Second, the early development and natural history of the disease should be understood sufficiently well to allow identification of parameters that measure its progression to disease. We now know that the pre-diabetic hyperglycaemic states, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), are stages in the early development toward diabetes.[19,233-235] Other parameters that are independently associated with the development of diabetes include age, family history of diabetes, waist-to-hip ratio, body mass index, blood pressure, and lipid levels. When taken together, these parameters, combined with plasma glucose levels, are more predictive of future diabetes than glucose levels by themselves.[236]

Third, there should be an available test to detect the pre-disease state that is safe, acceptable and predictive. This criterion is met by the use of fasting plasma glucose and the 2-hour glucose value in the oral glucose tolerance test. Fourth, there should be safe, effective, and reliable method(s) to prevent or at least delay the disease from occurring. Additionally, it is important to consider if the method employed to prevent the disease is able to confer additional benefits. In the case of diabetes, we would wish to know, for example, if the prevention method is able to positively impact cardiovascular disease.

Fifth, the preventive strategy should be economically acceptable. This means the effort to identify individuals who are at high risk of getting the disease, plus the cost of the intervention(s), should be cost-effective. This condition has not yet been clearly established for diabetes.

There are data that suggest that opportunistic screening (i.e. screening during routine encounters with health care personnel) is the most cost-effective way to find individuals at risk for diabetes.[237] However, no studies have been published on the cost-effectiveness of screening to detect pre-diabetes (IFG or IGT), or to prevent or delay the diagnosis of diabetes. Of even greater importance, it is unknown whether intervention at the stage of pre-diabetes (IFG or IGT) is a cost-effective way to prevent or delay the complications of diabetes, which are more relevant to the patient, family and society, than simply the diagnosis of diabetes.

There are other implications apart from financial implications. Individuals may respond negatively to a label of IFG or IGT, and some may face discrimination in the workplace, or by insurers. Also, intervention can promote anxiety and be socially disruptive.

13.1 Who are potential candidates for screening and intervention?

Current consensus information suggests that individuals who are at increased risk of developing diabetes may be identified by the current definitions of IFG and IGT.[238] The guidelines regarding the diagnosis of IFG and IGT are found in chapter 2.

13.2 How should diabetes prevention be effected?

Two early reports[230,239] suggested that lifestyle changes can prevent diabetes, but weaknesses in study design limit their relevance. In recent years, however, four well-designed randomised controlled trials have been published that address the issue of how type 2 diabetes may be prevented or delayed.

In the Finnish study,[240] 522 middle-aged, obese subjects (mean BMI 31 kg/m^2) with IGT were randomized to receive either brief diet and exercise counselling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on exercise (intervention group). The two groups were followed up for an average of 3.2 years. In the intervention group, there was a 58% relative reduction in the incidence of diabetes compared to the control group. A strong correlation was seen between non-progression to diabetes and the degree to which subjects were able to achieve one or more of the following: lose weight (goal of

5.0% of baseline weight), reduce saturated fat intake (goal of <10% of calories), increase fibre intake, exercise (goal of >150 minutes/week).

In the Diabetes Prevention Program,[241-243] the 3234 subjects had a mean age of 51 years, were more obese, but had nearly identical glucose tolerance compared to subjects in the Finnish study. Subjects were randomised to one of three intervention groups: an intensive nutrition and exercise counselling (lifestyle) group; a blinded metformin group; or a blinded placebo group. Subjects in the metformin and placebo group also received standard diet and exercise recommendations. After an average follow up of 2.8 years, a 58% relative reduction in the progression to diabetes was seen in the lifestyle group, a 31% relative reduction in the progression to diabetes was seen in the metformin group compared to control subjects.

In the STOP-NIDDM trial,[244,245] 1429 subjects with IGT were randomized, in double blind fashion, to receive either acarbose (an α-glucosidase inhibitor) or placebo. After a median follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was seen in the acarbose treated group compared with the control group. If the diagnosis was confirmed with a second OGTT, a 36% relative risk reduction was seen. The absolute risk reduction in the acarbose treated group was 9%.

In the Troglitazone in Prevention of Diabetes (TRIPOD) study,[246] 235 Hispanic women with previous gestational diabetes were randomized to receive either placebo or troglitazone. Troglitazone is now banned in most countries because of hepatotoxicity. It belongs to the thiazolidinedione class, to which two other commercially available drugs belong. After 30 months, troglitazone treatment was associated with a 56% relative reduction in progression to diabetes. After a washout period of more than 8 months, the 'preventive' effects of the drug were still observed. In the case of metformin and acarbose, the incidence of diabetes after discontinuation of the drug has not yet been determined, so it is unclear if they, too may have a true 'preventive' effect.

Of these four studies, only the Diabetes Prevention Program compared lifestyle modification against glucose-lowering pharmacological agents. It found that lifestyle modification was nearly twice as effective in preventing diabetes. This is an important finding. It also found that metformin had greater efficacy in preventing diabetes in younger, very obese individuals, compared to older, less overweight individuals.

It is crucial to remember that when drugs are used to delay or prevent type 2 diabetes in high risk individuals, regular monitoring for side effects is required.

The Micro-Hope study[7] provides data that ACE inhibitors may lower the risk of developing diabetes, but more studies are necessary before ACE inhibitors can be recommended for preventing diabetes.

In the XENDOS study,[247] orlistat was examined for its ability to delay type 2 diabetes when added to lifestyle change in subjects with BMI ≥ 30 kg/m^2 with or without IGT. After 4 years of treatment, the effect of orlistat addition corresponded to a 45% risk reduction in the IGT group, with no observed effect in those without IGT**.**

The greater benefit of weight loss and physical activity in preventing progression to diabetes strongly suggests that lifestyle modification should be the first-line treatment of choice for high risk pre-diabetic individuals.[238] Modest weight loss (5-10% of body weight) and increased physical exercise (3 to 5 days per week, 20 to 60 minutes each time) is recommended.

On current evidence, it is difficult to broadly or routinely recommend drug therapy to prevent or delay diabetes. First, in terms of absolute risk reduction, the studied drugs are less efficacious compared to lifestyle changes. Second, their efficacy appears to depend on subject phenotype, which means they may not be efficacious in all subjects. Third, whenever a drug is used, monitoring for side effects is required. Fourth, although there are emerging data in this area, none of the glucose-lowering drugs have been studied with regard to protection against cardiovascular disease in non-diabetic or pre-diabetic individuals. Fifth, prescribing a medication to delay the onset of diabetes, which is one that is also used to treat diabetes, increases a patient's total years of drug exposure. Finally, routinely using drugs to prevent or delay diabetes raises important issues of cost, and information from studies on cost-effectiveness is needed.[238]

13.3 Summary of recommendations

A Individuals at high risk for developing diabetes should be made aware of the benefits of even modest weight loss and participating in regular physical activity.

Grade A, Level Ib

B Screening for high risk individuals should be done opportunistically, with either a fasting plasma glucose test, or a 2-hour OGTT.

Grade B, Level IIb

A Persons with IGT or IFG should be given counselling about weight loss as well as instructions on how to increase physical activity.

Grade A, Level Ib

C Drug therapy should not be routinely used to prevent diabetes until more information, particularly in regard to cost-effectiveness, is available.

Grade C, Level IV

14 Cost-benefit Issues for Diabetes Mellitus

Diabetes mellitus is a costly condition, not just to the individual who has it, but also to healthcare systems with finite resources.[248] Macrovascular disease is the major component of the costs in type 2 diabetes, and this component is incurred much earlier than those accruing from managing microvascular complications. In the US, 52% of costs incurred may be attributed to the management of macrovascular disease, while nephropathy accounts for 21%, neuropathy 17%, and retinopathy 10%.[249] Reducing the risks of macrovascular complications should ease the costs of diabetes mellitus. Whether this results in net savings for the individual or the healthcare system concerned would then depend on the cost of the treatment used to achieve the lower risks.

Data concerning the cost and benefit of any treatment may be derived from either empirical studies, or from modelling studies of simulated populations. Modelling uses a set of formulae based on assumptions about the accuracy of screening methods, rates of disease progression to end-stage complications or death with and without a particular intervention, and the treatment costs. In chronic diseases like diabetes, empirical studies of interventions, for which outcomes would not be evident for many years, are seldom performed because of high costs and time delays. Much of current information comes from modelling studies which generate results rapidly, but are highly influenced by assumptions, and represent predictions rather than observations.

Improved glycaemic control

Type 1 diabetes

The Diabetes Control and Complications Trial (DCCT) demonstrated that improved glycaemic control intended to achieve near-normoglycaemia, compared with standard treatment in type 1 diabetes, could delay the progression of retinopathy, nephropathy, and neuropathy by about 50%.[10] An economic analysis by the DCCT Research Group concluded that for type 1 diabetes, the cost-effectiveness of improved glycaemic control is within the range considered to represent a good value.[250]

Type 2 diabetes

In a US economic analysis of improved glycaemic control for type 2 diabetes, intended to achieve normoglycaemia by keeping the HbA_{1c} at $\leq 7.2\%$, it was found that, for type 2 diabetes, the cost-effectiveness of improved glycaemic control is within the range of interventions that is generally considered cost-effective.[251]

Other interventions

Blood pressure control[252], blood lipid control[253], smoking cessation[254] and exercise[255] are four widely practised interventions to prevent cardiovascular disease. Economic analyses have shown that, for the general population, such practices are clearly cost-effective. For diabetic patients, however, cost-benefit analyses have not been reported, but it is not unreasonable to expect that these interventions would also be cost-effective.

15 Clinical Quality Indicators for Diabetes Mellitus

15.1 Introduction

Diabetes is a chronic illness with multiple serious complications. Evaluation of the effectiveness of existing diabetes services will aid clinical and managerial decision-making. Traditionally, randomized controlled trials (RCT), such as the Diabetes Control and Complications trial (DCCT), have been used to evaluate the efficacy of a single treatment. However, it is increasingly recognized that longitudinal observational studies complement RCT by addressing medical effectiveness, i.e. how well prevailing treatment works in clinical practice settings. Therefore, continuous multidimensional monitoring of the management of diabetes (i.e. monitoring of the quality of care) from which further improvements could be made, is desirable.

Many quality indicators have been proposed to measure different aspects of diabetes management.[256] These indicators include measures of ***structure*** (e.g. availability of a specialized diabetes centre and interdisciplinary diabetes health care (DHC) team, measures of ***process*** (e.g. measuring haemoglobin A_{1c}) and measures of ***outcome*** (e.g. end stage renal disease). The structure in a service refers to the environment of care. The process aspect of health services is how things are organized and done. Outcome is concerned with the impact of health services on individuals and communities. The dynamic relationship between process and outcome sometimes makes them inseparable.

This section is meant to be a resource for clinicians and administrators in primary health care (PHC). The workgroup feels that the process of care should be the main focus of this chapter since this is most relevant to family physicians who are our front-line diabetes care providers. In corollary, the workgroup believes that a quality assurance* and accreditation† process based on these key recommendations will aid in improving diabetes care in Singapore. However, the most appropriate quality indicators in a given setting would obviously differ depending on the issue under consideration.

Additional resources may be consulted.[75,257,258]

* *Quality assurance process is a clinical and managerial framework that commits staff to producing a systematic continuous process of evaluating agreed levels of care and service provision. Outcome related measurements have gained increasing attention because there is a growing body of evidence to suggest that outcomes research has the potential for maximizing quality of care and minimizing use of services in type 2 diabetes.*[259]

† *Accreditation is a formalized procedure by which an organization, discipline or individual is deemed to have met an agreed standard. Outcomes data from the Epidemiology and Disease Control Department, Ministry of Health, suggest that there has been a steady rise in number of patients admitted to hospitals for diabetes and its related complications since 1993. There has also been a parallel rise in the number of bed-days utilization in all hospitals for these patients over the same period of time.*[260] *Therefore, there is a need to study the effectiveness of diabetes care in the individual patient and in our nation systematically.*

15.2 Measurement of quality indicators

The workgroup has proposed the following schedule to allow patients and health care providers to better gauge their quality of care.

The care provided to each patient may be more adequately appropriated if he/she were categorised according to his/her risk of developing complications arising from diabetes. Two risk categories are proposed.

- An "at risk" individual may be defined as one who is stable and meeting targets of control as agreed by the patient and his primary care physician.

- A "high risk" individual may be defined as:
  1. one whose control has been unstable and failing to meet targets in the past 12 months
  2. any pregnant female with diabetes
  3. one already with established diabetic complications
  4. one with psychosocial problems (including alcohol or substance abuse) that complicate management

Quality indicators	Recommended frequency*
HbA_{1c}	At risk: 6-monthly High risk: 3-4 monthly
Eye assessment	At risk: annual High risk: as clinically indicated
Foot assessment	At risk: annual High risk: as clinically indicated
Nephropathy assessment	At risk: annual High risk: as clinically indicated
Blood pressure measurement	At risk: 3-4 monthly High risk: as clinically indicated
Weight and BMI	At risk: 3-4 monthly High risk: as clinically indicated
Lipid profile	At risk: annual High risk: as clinically indicated
Cardiac assessment	At risk: as clinically indicated High risk: as clinically indicated
Self-management education	At risk: annual High risk: as clinically indicated

* includes a baseline assessment.

A sample of a patient care card is shown in Table 19 (page 123) to assist both the patient and his/her health care provider in the tracking of these indicators.

Monitoring of diabetes care quality indicators is an evolving and promising faculty. The precise value of some of the proposed measurements requires further research. Their implementation will require a concerted effort from all levels of health care providers.

15.3 Summary of recommendations

A Measures of process of diabetes care should include the initial and ongoing performance of medical indicators which have been proven to influence long-term outcome.

Grade A, Level Ib

GPP Data to measure the outcomes of diabetes management should be obtained from the individual with diabetes.

GPP

Table 19 A sample of a Patient Care Card: A 5-year record

Patient Care Card

Parameter	Date	Status	Date	Status	Date	Status
BMI (weight)						
Smoke						
Exercise						
Diabetes-specific education						
LDL-cholesterol (mmol/l)						
HDL-cholesterol (mmol/l)						
TG (mmol/l)						
SBP (mmHg)						
DBP (mmHg)						
HbA_{1c} (%)						
Serum Creatinine (umol/l)						
Urine albumin/protein						
Heart						
Eye						
Feet						
Anti-platelet therapy						

Sample of how the patient care card may be used

A 55-year old Indian male businessman with BMI of 34, smoker, no family history;
TYPE 2 DIABETES MELLITUS since 2002 - glibenclamide 5 mg om
BP 120/80 Weight 100kg, Height 1.7m
LDL 3.4 TG 2.8 HDL 0.9 HbA_{1c} 12%, urine protein 1+, s Cr 80

Patient Care Card

Parameter	Date	Baseline	Date	Status	Date	Status
BMI	09-07-2005	34 (100kg) target: BMI 28 (82kg)	13-11-2005	97 kg		
Smoke	09-07-2005	yes advised to stop	13-11-2005	yes advised to stop		
Exercise	09-07-2005	no start walking		started walking		
Diabetes-specific education	09-07-2005	overview				
LDL-cholesterol (mmol/l)	09-08-2005	3.4 start statin	13-11-2005	2.5		
HDL-cholesterol (mmol/l)	09-08-2005	0.9	13-11-2005	1.1		
TG (mmol/l)	09-08-2005	2.8	13-11-2005	1.8		
SBP (mmHg)	09-07-2005	120	13-11-2005	116		
DBP (mmHg)	09-07-2005	80	13-11-2005	78		
HbA_{1c} (%)	09-07-2005	12	13-11-2005	9.5		
Serum Creatinine (umol/l)	09-07-2005	80				
Urine albumin/protein	09-07-2005	1+	13-11-2005	negative		
Heart	09-12-2005	ECG - N				
Eye	09-07-2005	no eye appt	13-11-2005	Normal		
Feet	09-12-2005	skin, pulses - OK advice				
Anti-platelet therapy	09-07-2005	no	13-11-2005	yes		

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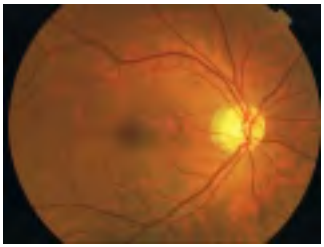
Annex 1 Photographs

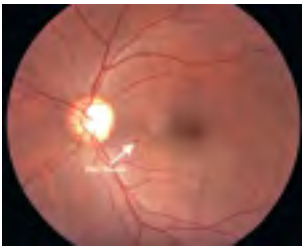
Figure 1



Features
No diabetic retinopathy.

Management
Annual eye examination.

Figure 2



Features
Mild non-proliferative diabetic retinopathy. Dot haemorrhage seen.

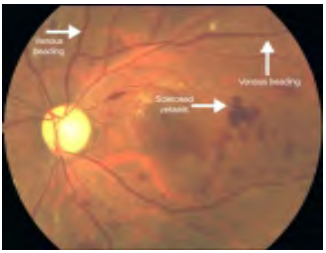
Management
6-12 monthly eye examination.

Figure 3

Features
Moderate non-proliferative diabetic retinopathy showing multiple dot/blot haemorrhages. These lesions appear dark and are better seen under green light.

Management
3- to 6-monthly eye examination depending on severity. Photo-coagulation in special situations such as significant co-existing cataract.

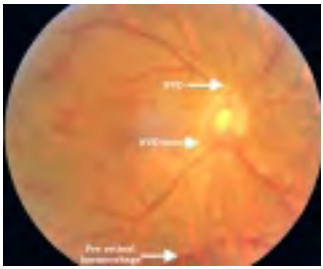
Figure 4



Features
Severe non-proliferative diabetic retinopathy showing congested and tortuous veins (venous beading) and sclerosed (“ghost”) vessels.

Management
Photocoagulation is indicated.

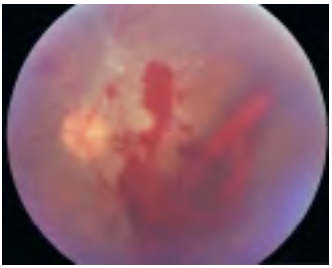
Figure 5



Features
Proliferative diabetic retinopathy showing new vessels or neo-vascularisation of the optic disc (NVD). The risk of vitreous haemorrhage is high.

Management
Photocoagulation as soon as possible.

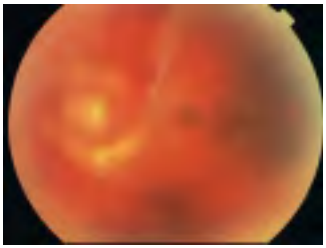
Figure 6



Features
Proliferative diabetic retinopathy with vitreous haemorrhage. The patient presented with decreased vision and sudden onset of multiple floaters.

Management
Photocoagulation on an urgent basis to areas not obscured by the haemorrhage.

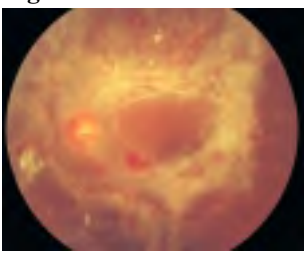
Figure 7



Features
Sudden decreased vision from a total vitreous haemorrhage.

Management
Vitreous haemorrhage, if mild, may resolve with time. Vitrectomy may sometimes be indicated for non-resolving vitreous haemorrhage.

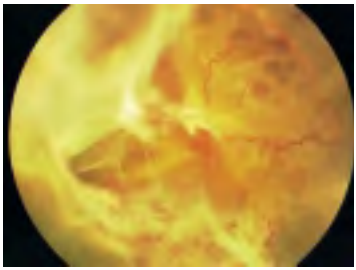
Figure 8



Features
Traction retinal detachment (advanced proliferative diabetic retinopathy) involving the macula. Vision is severely affected.

Management
Vitrectomy is aimed at preserving navigational vision but is more difficult in late presentations such as this.

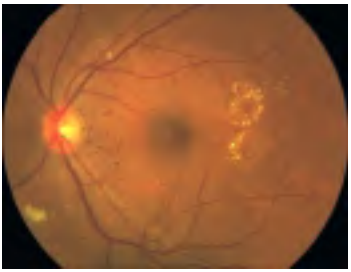
Figure 9



Features
Severe traction retinal detachment from advanced proliferative retinopathy. Vision is very poor.

Management
Visual loss is likely to be irreversible in such late presentations.

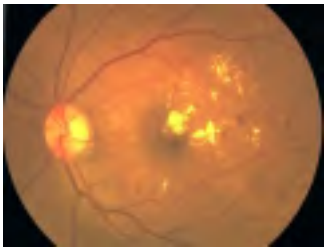
Figure 10



Features
Macular oedema (maculopathy) associated with moderate non-proliferative diabetic retinopathy. The macula is not imminently threatened by hard exudates.

Management
Photocoagulation can be delayed unless close follow-up is not possible. On average, 3- to 4-monthly retinal checks are needed.

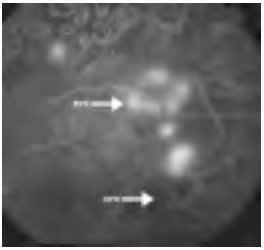
Figure 11



Features
Severe macular oedema (maculopathy) affecting the edge of the macula. Vision may still be good despite the risk of imminent visual loss.

Management
Photocoagulation is indicated. Sight-threatening retinopathy such as macular oedema can be present despite good vision.

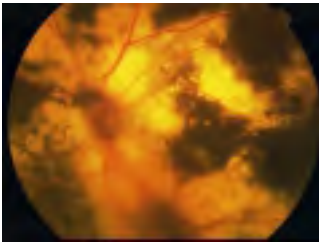
Figure 12



Features
Fundal fluorescein angiography showing peripheral neovascularisation or NVE (new vessels "elsewhere") and capillary fall-out (CFO) or non-perfusion.

Management
Photocoagulation indicated as soon as possible.

Figure 13



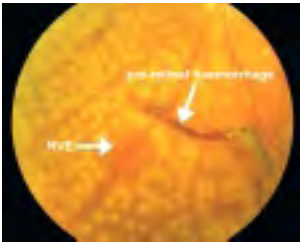
Features

Very severe and massive exudation such as this can occur after rapid normalisation of blood glucose in a patient with previously undiagnosed or poorly controlled diabetes.

Management

The retina should be assessed prior to restoration of poorly controlled blood glucose to normoglycaemic levels except in emergency situations.

Figure 14



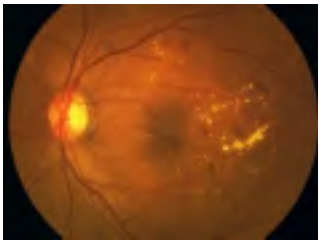
Features

Laser photocoagulation marks seen in an eye with proliferative diabetic retinopathy and preretinal haemorrhage.

Management

Multiple outpatient laser photo-coagulation sessions are needed for this stage of proliferative diabetic retinopathy.

Figure 15



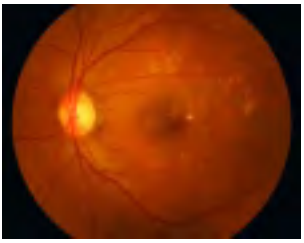
Features

Moderate macular oedema (maculopathy). A ring of hard exudates near the edge of the macula is present.

Management

Focal laser photocoagulation is indicated.

Figure 16



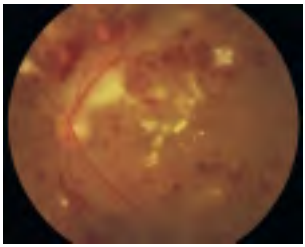
Features

Significant resolution of macular oedema and hard exudates following focal laser photocoagulation treatment.

Management

Regular follow-up is needed as recurrence of diabetic retinopathy lesions can still occur.

Figure 17



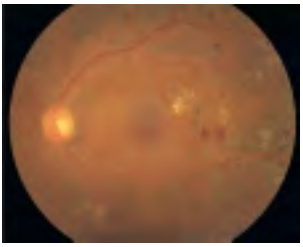
Features

Severe macular oedema involving the centre of the macula (fovea).

Management

Both grid laser and panretinal photocoagulation are indicated. The panretinal photocoagulation in this eye is titrated over a few sessions to avoid aggravating the macular oedema.

Figure 18



Features

Significant resolution of macular oedema after multiple laser photocoagulation sessions. Vision may not be fully restored in a late presentation such as this.

Management

A holistic approach and further assessment for other systemic risk factors such as diabetic nephropathy and dyslipidaemia are indicated.

* Photographs courtesy of Dr Yeo Kim Teck, Singapore National Eye Centre.

Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose the best answer.

1) The following are known to affect the progression of diabetic retinopathy
   A) blood glucose
   B) blood pressure
   C) anaemia
   D) pregnancy
   E) all of the above

2) All the statements are true of diabetic macular oedema except:
   A) It is always symptomatic
   B) It is a common cause of visual impairment
   C) It can be aggravated by hyperlipidaemia
   D) Laser therapy may not improve vision especially in late cases
   E) It can be associated with other stages of retinopathy

3) With regards to blood pressure control in diabetics, data from the UKPDS showed that for every 10 mm reduction in blood pressure there is a corresponding ____ reduction in the risks of diabetic retinopathy
   A) 5.2%
   B) 52%
   C) 75%
   D) 13%
   E) 3.3%

4) In a newly diagnosed obese type 2 diabetic patient who has symptomatic hyperglycaemia, the preferred initial treatment is:
   A) Metformin
   B) A short-acting non-sulfonylurea secretagogue
   C) Alpha-glucosidase inhibitor
   D) Insulin
   E) Lifestyle measures alone

5) The following statements regarding insulin therapy are correct except:
   A) All patients with type 1 diabetes will require insulin therapy.
   B) A significant proportion of patients with type 2 diabetes will eventually require insulin therapy.
   C) Multiple daily injections involving basal and bolus insulin are applicable for patients with either type 1 or type 2 diabetes.
   D) The rapid-acting insulin analogues should be injected 30 minutes before meals.
   E) The long-acting insulin analogues can be administered at any time of the day because of its pharmacokinetics in providing a smooth, peakless profile.

6) In a pregnant woman with diabetes, _____ during pregnancy is necessary to prevent complications like macrosomia, polyhydramnios, sudden unexplained fetal death and neonatal hypoglycaemia.
   A) tight control of blood sugar levels
   B) exercise
   C) fetal monitoring
   D) early delivery

7) Six weeks after delivery,
   A) all women should have an OGTT.
   B) all women with diabetes when they were pregnant should have an OGTT.
   C) all women who had gestational diabetes should have an OGTT.
   D) there is no need for a repeat OGTT in the postnatal period.

8) Which of the following statement is true
   A) metformin does not cause significant weight gain when used in obese individual with type 2 diabetes.
   B) combining sulphonylurea and repaglinide is a good synergistic therapeutic option.
   C) sulphonylureas must be used with caution in the presence of renal or hepatic insufficiency as it may cause lactic acidosis.
   D) the blood pressure target in persons with type 2 DM should be 130/80 mmHg.

9) Which statement is false concerning type 1 diabetes in childhood:
   A) A 7-year old girl with type 1 diabetes mellitus is best managed by a multi-disciplinary team in an institution.
   B) If the fasting blood glucose level is < 4 mmol/l, the possibility of antecedent nocturnal hypoglycaemia should be considered.
   C) Post-prandial administration of Lispro is as safe and effective as pre-prandial regular insulin.
   D) Glargine is the insulin of choice for pre-school children.
   E) The target pre-meal blood glucose level for a child < 6 years ranges from 5-12 mmol/l.

10) A 15-year old obese boy who has just been diagnosed to have type 2 diabetes, has a random blood glucose level of 13 mmol/l. In addition to diet and exercise, the initial recommended treatment is to commence:
   A) Insulin
   B) Metformin
   C) Glipizide
   D) Acarbose
   E) Troglitazone

Answer

1. E (79)
2. A (78,81-85)
3. D (81)
4. A (37)
5. D (43-45)
6. A (100)
7. C (103)
8. A (37,39,59)
9. D (107-109)
10. B (110)

Workgroup Members

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MOH CLINICAL PRACTICE GUIDELINES 3/2006

Diabetes Mellitus

Ministry of Health

Diabetic Society of Singapore

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Diagnosis and Screening of Diabetes Mellitus in Singapore

B In subjects with unequivocal hyperglycaemia with acute metabolic decompensation diabetes mellitus can be diagnosed without further testing (pg 20).

Grade B, Level III

B In patients with typical symptoms, diabetes mellitus can be diagnosed if any one of the following is present:

1. Casual plasma glucose ≥11.1 mmol/l
2. Fasting plasma glucose ≥7.0 mmol/l
3. 2-hour post-challenge glucose ≥11.1 mmol/l

Other individuals should have a repeat test on a subsequent day (pg 20).

Grade B, Level III

B Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus (pg 20).

Grade B, Level III

B We should recognise intermediate states of glucose metabolism termed impaired fasting glycaemia and impaired glucose tolerance in accordance with the report of the WHO consultation (pg 21).

Grade B, Level III

B All subjects with fasting plasma glucose from 6.1 to 6.9 mmol/l should undergo a 75 g oral glucose tolerance test to determine if they have impaired glucose tolerance or diabetes mellitus (pg 21).

Grade B, Level III

C Screening of asymptomatic individuals for diabetes mellitus should be carried out in accordance with the Ministry of Health Clinical Practice Guidelines for Health Screening (6/2003).

Grade C, Level IV

N.B. The workgroup recommends lowering the cut-off value of triglycerides at which the individual is considered at increased risk of diabetes from 2.82 in MOH Clinical Practice Guidelines on Health Screening to 2.30 mmol/l (pg 22).

Lifestyle Modification

B Lifestyle modification is a cornerstone of diabetes management. Medical nutrition therapy and exercise prescription should be the initial therapy in obese (BMI $\geq$ 30) and overweight (BMI $\geq$ 25) type 2 diabetic patients unless they are symptomatic or severely hyperglycaemic (pg 31).

Grade B, Level IIa

C Medical nutrition therapy should be individualized. Saturated fat intake should not exceed 10%, with carbohydrates making up 50-60% and proteins 15-20% of total calorie intake. Diet should include foods from each of the basic food groups (pg 31).

Grade C, Level IV

C An exercise programme tailored to suit the individual's age, fitness, aptitude and interest should be prescribed (pg 32).

Grade C, Level IV

C A pre-exercise evaluation to identify macrovascular, microvascular and neurological complications is recommended (pg 32).

Grade C, Level IV

C Individuals with diabetes, especially those on insulin treatment, should receive specific education on the prevention of exercise-induced hypoglycaemia (pg 32).

Grade C, Level IV

C Individuals with diabetic neuropathy should avoid exercises associated with repetitive foot trauma (pg 33).

Grade C, Level IV

C Individuals with severe diabetic proliferative retinopathy should avoid activities that dramatically elevate blood pressure (pg 33).

Grade C, Level IV

B Individuals with diabetes should be discouraged from smoking (pg 33).

Grade B, Level III

B Diabetic patients with poor glycaemic control or dyslipidaemia should be discouraged from consuming alcohol (pg 33).

Grade B, Level IIb

Pharmacotherapy in Diabetes Mellitus

A Type 2 diabetic patients may initially be treated with lifestyle modification (diet and exercise) for 2 to 4 months unless they are symptomatic or severely hyperglycaemic (i.e. random blood glucose >15 mmol/l or fasting blood glucose >10 mmol/l). Oral antihyperglycaemic agents should be started if glycaemic targets are not achieved. Insulin therapy should be started, if optimal combination therapy, fails to attain target control (i.e. 2 consecutive HbA_{1c} values failed to reach ≤8% over 3-6 months interval) (pg 36).

Grade A, Level Ia

A Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes. Stepwise therapy with multiple pharmacological therapies is often needed over time to maintain target glucose control. Two or more oral agents, or insulin therapy either alone or in combination with oral agents, may be required (pg 35).

Grade A, Level Ia

A All type 1 diabetic patients must receive insulin. Multiple daily injections (3 or more) or the use of continuous subcutaneous insulin infusion (CSII or insulin pump therapy) may be required to achieve target glucose levels (pg 44).

Grade A, Level Ib

Glycaemic Control: Assessment and Targets

GPP Health care professionals should be familiar with the practical use of glucometers (pg 48).

GPP

B Self-monitoring of blood glucose (SMBG) should be initiated in most patients with diabetes, especially in insulin-treated subjects, in pregnant women with pre-existing diabetes or gestational diabetes, and in patients who are at increased risk of developing hypoglycaemia (pg 48).

Grade B, Level IIa

GPP The visual method of self-monitoring of blood glucose is not recommended (pg 49).

GPP

A Besides receiving proper training in the use of blood glucometers, patients must be educated on the interpretation of the results and, where possible, taught to modify treatment according to blood glucose levels (pg 50).

Grade A, Level Ib

C Testing for glucose in urine is not recommended for monitoring of glycaemic status (pg 50).

Grade C, Level IV

C Testing for ketones in the urine is recommended in patients with type 1 diabetes, pregnant women with pre-existing and gestational diabetes, if there is:

- Acute illness or stress
- Persistent elevation of blood glucose (>16.7 mmol/l)
- Any symptom suggestive of ketoacidosis (nausea, vomiting, abdominal pain or acetone breath) (pg 51).

Grade C, Level IV

GPP Routine monitoring of blood ketones is not recommended for type 1 or type 2 diabetic patients (pg 51).

GPP

C Glycated haemoglobin (HbA_{1c}) testing should be performed routinely in all patients with diabetes. The frequency of testing for any individual patient may vary according to the treatment regimen used and the status of glycaemic control (pg 52).

Grade C, Level IV

C The following schedule is recommended for glycated haemoglobin testing:

- 3- to 4-monthly in patients with unstable glycaemic control, failure to meet treatment goals, recent adjustment in therapy, or intensive insulin therapy.
- 6-monthly in patients who have stable glycaemic control and who are meeting treatment goals (pg 52).

Grade C, Level IV

C The targets of glycaemic control should be defined for each patient, with patient participation in the process (pg 53).

Grade C, Level IV

A "Optimal" glucose control should be the target for the majority of patients with diabetes. This refers to glucose levels that approach the normal range (HbA_{1c} 6.5-7.0%; preprandial glucose 6.1-8.0 mmol/l) and is associated with a low risk of developing microvascular complications (pg 53).

Grade A, Level Ib

A "Suboptimal" glucose control (HbA_{1c} 7.1-8.0%; preprandial glucose 8.1-10.0 mmol/l) may be the target in special subsets of patients who are vulnerable to injury from the increased risk of severe hypoglycaemia associated with "optimal" glucose control (pg 53).

Grade A, Level Ib

Prevention of Cardiovascular Disease in Diabetes Mellitus

GPP The assessment of cardiovascular risk in persons with type 2 diabetes mellitus should include:

1. A medical history, which should include:
   a. A smoking history.
   b. A history of hypertension and/or medication taken for the treatment of hypertension.
   c. A history of pre-existing cardiovascular disease (CVD) to include angina pectoris, myocardial infarction, stroke, or peripheral vascular disease.
2. A physical examination which should include an assessment of peripheral pulses.
3. Blood pressure should be measured each time a patient with type 2 diabetes mellitus is seen in the clinic.
4. Fasting serum lipids should be measured at the time of diagnosis and at least once a year if they are in the optimal range.
5. Assessment of urine for microalbuminuria or proteinuria should be carried out at the time of diagnosis and at least once a year in all patients.
6. In view of the fact that persons with type 2 diabetes mellitus are more likely to experience atypical symptoms of coronary heart disease (CHD), a routine resting ECG is recommended at baseline. Subsequent ECG may be performed when clinically indicated. Specific abnormalities which may suggest CHD should be assessed by a cardiologist for appropriate risk stratification (page 57).

GPP

B The primary prevention of CVD should form one of the major goals of therapy in the management of type 2 diabetes mellitus (pg 57).

Grade B, Level III

B Type 2 diabetes mellitus should be considered a coronary CHD risk equivalent (pg 57).

Grade B, Level III

C An assessment of the CVD risk factors present is recommended for all persons with type 2 diabetes mellitus in order that appropriate therapy be instituted (pg 57).

Grade C, Level IV

A The prevention of CVD in persons with type 2 diabetes mellitus must take a global approach with intervention targeting all aspects of the disease (pg 58).

Grade A, Level Ib

C Therapeutic lifestyle modification (through modulation of diet and physical activity) should form the mainstay of strategies to reduce cardiovascular risk associated with type 2 diabetes mellitus (pg 58).

Grade C, Level IV

B All possible efforts should be taken to encourage persons with type 2 diabetes mellitus to stop smoking (pg 59).

Grade B, Level III

Hypertension in patients with diabetes mellitus

A The target of hypertension treatment in type 2 diabetes mellitus should be < 130/80 mmHg (pg 59).

Grade A, Level Ib

A Lifestyle modification and drug therapy should be instituted for all subjects with blood pressure >130/80 mmHg (pg 59).

Grade A, Level Ib

A The choice of first line therapy can include (a) diuretics (D) (b) β-blockers (BB) (c) ACE inhibitors (ACEI) (d) calcium channel blockers (CCB) (e) angiotensin II receptor blockers (ARB) and should be based on the cost of the drug and any compelling indications and contraindications for its use (pg 60).

Grade A, Level Ib

Dyslipidaemia in patients with diabetes mellitus

A For the prevention of CVD, the first priority is optimization of the LDL cholesterol. This is followed by HDL-cholesterol and then triglyceride (pg 63).

Grade A, Level Ia

C The exception is in individuals with levels of TG >4.5 mmol/l (400 mg/dl) who have an increased risk of acute pancreatitis. In these patients, the first priority is to reduce the TG level to prevent acute pancreatitis (pg 63).

Grade C, Level IV

C Fibrate therapy should be considered as first line therapy in those with TG > 4.5 mmol/l (400 mg/dl) to prevent acute pancreatitis (pg 63).

Grade C, Level IV

A For all other patients with type 2 diabetes mellitus and LDL cholesterol >2.6 mmol/l (100 mg/dl), the treatment of choice is an HMG CoA reductase inhibitor (statin) (pg 63).

Grade A, Level Ia

A For patients with LDL cholesterol <2.6 mmol/l (100 mg/dl) and low HDL-cholesterol (<40 mg/dl), a fibrate can be started as the initial lipid lowering therapy (pg 63).

Grade A, Level Ib

C If HDL cholesterol remains low (<1 mmol/l or 40 mg/dl) after achieving the LDL goal with a statin, combination therapy can be considered in selected high risk patients, such as those with type 2 diabetes mellitus and existing CHD (pg 63).

Grade C, Level IV

B When combining a statin with a fibrate, gemfibrozil should not be used (pg 64).

Grade B, Level III

Anti-thrombotic agents in patients with diabetes mellitus

A All patients with type 2 diabetes mellitus over the age of 45 years or who have concomitant hypertension, dyslipidaemia or pre-existing cardiovascular disease (CHD, stroke or peripheral arterial disease) should be treated with aspirin 75-100 mg per day. In the presence of contraindications for aspirin therapy, other antiplatelet agents such as clopidogrel may be a reasonable alternative for patients with high risk (pg 64).

Grade A, Level Ia

Prevention and Treatment of Diabetic Nephropathy

C Screening for albuminuria should begin at 5 years after the diagnosis of type 1 diabetes; it should, however, begin immediately with the diagnosis of type 2 diabetes. Thereafter, screening for albuminuria should be done annually (pg 70).

Grade C, Level IV

GPP Serum creatinine should be measured at least annually (pg 70).

GPP

C The blood pressure target in all diabetic persons should be less than 130/80 mmHg. Diabetic patients with proteinuria levels exceeding 1 gram should try to have their BP lowered to less than 125/75 mmHg (pg 72).

Grade C, Level IV

A In the absence of microalbuminuria or overt nephropathy, the principal intent is that of reducing the risk of a cardiovascular event. There is evidence for the initial antihypertensive agent to be from one of these classes: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers, diuretics, calcium channel blockers (pg 73).

Grade A, Level Ib

A In the presence of microalbuminura, both ACE inhibitors and ARBs can be used (pg 73).

Grade A, Level Ib

A In the presence of overt nephropathy in type 1 diabetes, there is evidence that an ACE inhibitor can retard the progression of otherwise progressive renal disease (pg 74).

Grade A, Level Ib

A In type 2 diabetes with overt nephropathy, either an ACE inhibitor or an ARB may be used to retard the progression of renal disease (pg 74).

Grade A, Level Ib

GPP The serum creatinine and potassium should be checked within 4 weeks of initiation of treatment to detect any rise in the serum creatinine or hyperkalaemia (pg 74).

GPP

GPP Progressive but non-continuous rise in the serum creatinine may be seen over 2 to 3 months after starting on ACE inhibitor or ARB. A short-term rise of less than 30% in the serum creatinine should not necessitate withdrawing the ACE inhibitor or ARB. Nevertheless, the possibility that there may be critical renal artery stenosis should be considered, especially in the presence of a renal artery bruit or refractory hypertension or asymmetric kidney sizes on ultrasound (pg 74).

GPP

GPP Therapy should aim to reduce albuminuria as much as possible, and it is reasonable to aim for a proteinuria target of less than 1 g/day or at least 50% of the pre treatment value (pg 75).

GPP

GPP Type 1 diabetic patients with overt nephropathy should be maintained on a low protein diet of 0.8 g/kg/day (pg 75).

GPP

GPP A nephrology referral is recommended when there are unexpected or rapid decline in renal function, difficulties with hyperkalaemia, atypical features e.g. haematuria, presence of casts in the urine sediment, presence of a renal bruit, difficult BP control, nephrotic range proteinuria (>3 g/day), and absence of retinopathy (pg 75).

GPP

Prevention and Management of Eye Complications

Screening

C All patients diagnosed with diabetes require regular visual acuity assessment and eye examinations by trained personnel to screen for diabetic retinopathy using a test of adequate sensitivity (pg 78).

Grade C, Level IV

C Type 1 diabetic patients should be examined 3-5 years after diagnosis of diabetes, and at least once yearly subsequently. Type 2 diabetic patients should have an ocular assessment at the time of diagnosis and at least once yearly subsequently (pg 79).

Grade C, Level IV

C Retinal screening preferably using retinal photography, or direct ophthalmoscopy (if retinal photography is not available) through dilated pupils is recommended (pg 78).

Grade C, Level IV

Management of systemic risk factors

A Good glycaemic control (HbA_{1c} preferably 6.5 to 7.5%) should be instituted to reduce the risk of retinopathy (pg 80).

Grade A, Level Ib

A Good control of blood pressure at or below 130/80 mmHg should be instituted to reduce the progression of diabetic retinopathy (pg 81).

Grade A, Level Ib

C Significant hyperlipidaemia should be treated to retard diabetic retinopathy (pg 81).

Grade C, Level IV

Referrals

GPP Diabetic patients found to have diabetic retinopathy by their physicians should be referred for further ophthalmological assessment (pg 84).

GPP

A Timely laser therapy should be offered to patients with proliferative diabetic retinopathy and diabetic macular oedema. Panretinal and focal/grid laser treatment results in at least a 50% reduction in the risk of visual loss (pg 85).

Grade A, Level Ib

Treatment

A Laser photocoagulation should be instituted for severe and proliferative retinopathy as it produces a 50% reduction in risk for severe visual loss and need for vitrectomy (pg 85).

Grade A, Level Ib

Prevention of Diabetic Foot Complications

B All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions (pg 92).

Grade B, Level IIb

B The assessment of the feet involves risk identification, treatment and patient education appropriate to the level of risk (pg 92).

Grade B, Level IIa

A All patients, regardless of risk category, should receive ongoing education on footcare and footwear advice (pg 93).

Grade A, Level lb

B Patients identified with foot-related risk conditions should have access to a specialized footcare team which should include diabetes specialist, podiatrist, physiotherapist trained in diabetes, diabetes nurse educator and vascular and orthopaedic surgeon (pg 93).

Grade B, Level III

A Urgent referral to a specialized footcare team is needed in the presence of ulcerations, severe foot infection and gangrene (pg 91).

Grade A, Level Ib

Management of Women with Pregestational and Gestational Diabetes Mellitus

Preconception care

B All diabetic women in the reproductive age group should receive pre-pregnancy counselling, particularly before starting a family (pg 98).

Grade B, Level IIa

Screening and diagnosis

B Women at high-risk for gestational diabetes (GDM) should undergo an OGTT as early in pregnancy as feasible. Re-evaluation may be necessary at 28 weeks if glucose intolerance is not present at the early screen (pg 99).

Grade B, Level IIa

B In all other patients, urine for glucose should be obtained at each antenatal visit and random blood sugar levels ascertained when there is ≥1+ glycosuria. A diagnostic test is necessary if the random plasma blood glucose >6.6 mmol/l more than 2 hours after a meal, or >7.0 mmol/l within 2 hours of a meal (pg 99).

Grade B, Level III

Antenatal care

B In gestational diabetes (GDM), dietary control should be used in the first instance to attain glycaemic goals. If nutritional therapy does not consistently maintain a fasting or pre-meal capillary blood glucose of <5.5 mmol/l and/or a 2-hour postprandial capillary blood glucose of <6.7 mmol/l on two or more occasions within a 1-2 week interval, insulin therapy should be considered (pg 100).

Grade B, Level IIa

B In established diabetics (pregestational diabetes), intensive insulin treatment is often necessary to maintain target blood glucose levels (pg 100).

Grade B, Level IIb

B Maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting or premeal state, and/or <7.8 mmol/l 1 hour after meals, and/or <6.7 mmol/l 2 hours after meals (pg 100).

Grade B, Level III

B All women diagnosed with GDM and pregestational DM should receive specialized care (pg 100).

Grade B, Level III

Infants of diabetic mothers

B Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life. Infants of diabetic mothers should be fed early (pg 103).

Grade B, Level III

Postnatal management

B Breastfeeding is not contraindicated in women with diabetes (pg 103).

Grade B, Level III

B An OGTT should be performed at least 6 weeks postpartum and the patient reclassified and counselled according to criteria accepted in the non-pregnant state (pg 103).

Grade B, Level IIb

Contraception

B Low dose oestrogen-progestin oral contraceptives and the intra-uterine contraceptive devices are not contraindicated in women with previous GDM (pg 104).

Grade B, Level III

B Oestrogen-progestogen contraceptives should be avoided in women with complications of diabetes and those at risk of vascular disease (pg 104).

Grade B, Level III

Management of the Child and Adolescent with Diabetes Mellitus

B In childhood type 1 diabetes mellitus, the aims of treatment are:

a. Normal physical growth and pubertal development.
b. Normal psychosocial development and full participation in age-appropriate activities.
c. Good glycaemic control with minimal hypoglycaemia.
d. Absence of diabetic ketoacidosis.
e. Minimization and early detection and treatment of complications (pg 107).

Grade B, Level IIa

B The care of diabetes in childhood and adolescence, whether type 1 or type 2, is best accomplished by a multi-disciplinary team in an institutional setting (pg 107).

Grade B, Level IIa

B Screening for diabetes should be considered for children and adolescents who are overweight, have a strong family history of diabetes and have acanthosis nigricans, hypertension, dyslipidaemia or the polycystic ovarian syndrome. Testing in these individuals should be done at least every 2 years starting from age 10 years or at the onset of puberty, if the latter occurs at a younger age (pg 109).

Grade B, Level IIa

C Children and adolescents with impaired glucose tolerance and obesity should be managed with diet and exercise (pg 111).

Grade C, Level IV

C Children with type 2 diabetes mellitus may initially be treated with lifestyle modifications (diet and exercise), unless they are symptomatic or severely hyperglycaemic (pg 110).

Grade C, Level IV

C Oral hypoglycaemic agents may be started in children with type 2 diabetes if glycaemic targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control (pg 110).

Grade C, Level IV

Prevention of Type 2 Diabetes

A Individuals at high risk for developing diabetes should be made aware of the benefits of even modest weight loss and participating in regular physical activity (pg 116).

Grade A, Level Ib

B Screening for high risk individuals should be done opportunistically, with either a fasting plasma glucose test, or a 2-hour OGTT (pg 114).

Grade B, Level IIb

A Persons with impaired glucose tolerance or impaired fasting glucose should be given counselling about weight loss as well as instructions on how to increase physical activity (pg 116).

Grade A, Level Ib

C Drug therapy should not be routinely used to prevent diabetes until more information, particularly in regard to cost-effectiveness, is available (pg 116).

Grade C, Level IV

Clinical Quality Indicators for Diabetes Mellitus

A Measures of process of diabetes care should include the initial and ongoing performance of medical indicators which have been proven to influence long-term outcome (pg 122).

Grade A, Level Ib

GPP Data to measure the outcomes of diabetes management should be obtained from the individual with diabetes (pg 122).

GPP

Flowchart for the diagnosis of diabetes mellitus

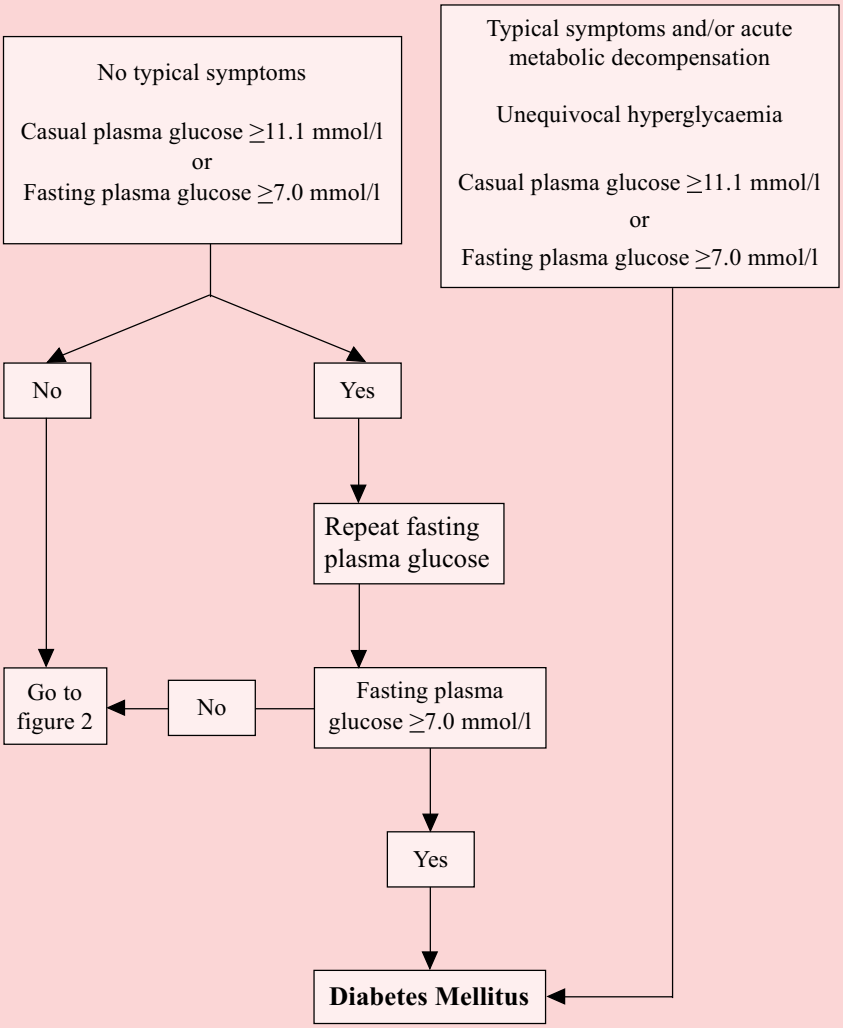

Figure 2 Flowchart for individuals suspected to have diabetes but whose fasting plasma glucose <7.0 mmol/l