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MINISTRY OF HEALTH
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Diabetes Mellitus

MOH Clinical Practice Guidelines 1/2014

Academy of Medicine, Singapore

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Chapter of Endocrinologists College of Physicians, Singapore

College of Family Physicians, Singapore

Diabetic Society of Singapore

Singapore Medical Association

Endocrine and Metabolic Society of Singapore

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CLINICAL PRACTICE GUIDELINES

Diabetes Mellitus

MOH Clinical Practice Guidelines 1/2014

Addendum

These guidelines were initially available on the MOH website on 25 May 2014. This updated version is published on 25 July 2014. Based on the feedback received, the grades of two recommendations and the blood pressure clinical quality indicator have changed.

On page 141 of full CPG document (and page 27 of the summary booklet)

D Infants of women with diabetes who present with clinical signs of hypoglycaemia should have their blood glucose tested and be treated with intravenous dextrose as soon as possible.[312] Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life.

Grade D, Level 4

On page 142 of full CPG document (and page 27 of the summary booklet)

D 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. [312]

Grade D, Level 4

On page 165 of full CPG document (and page 35 of the summary booklet)

Blood pressure	Percentage of patients with most recent blood pressure <140/80mmHg

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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.

Contents

Foreword

The rising incidence of diabetes mellitus is an issue of global concern. The World Health Organisation has consistently identified diabetes mellitus as one of the main causes of death globally for the last decade. Here in Singapore there has been an increase in the proportion of people affected by diabetes from 8.2% in 2004 to 11.3% in 2010* with diabetes becoming Singapore's tenth leading cause of death. This growing prevalence will present Singapore with a range of challenges across our health system.

Singapore's clinicians need to offer a strong response against this disease based on prevention, early diagnosis and aggressive initial treatment. Such a response not only delays the progression of diabetes itself but also other associated chronic complications such as coronary heart disease, retinopathy and nephropathy. Clinicians have the opportunity to significantly improve the morbidity and mortality of their patients with diabetes, if they manage their patients' condition appropriately.

These guidelines should provide clinicians with the latest best practice information regarding how to manage diabetes particularly in primary care. The workgroup has carried out a thorough review of literature to formulate these guidelines particularly regarding pharmacological interventions. These guidelines also provide guidance on a range of non-pharmacological interventions including medical nutrition therapy which is an important aspect of diabetes care.

I am sure these updated guidelines will assist doctors and other clinicians in improving the management of patients with diabetes.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

* Ministry of Health, Singapore. National Health Survey 2010, Singapore. Singapore: Epidemiology and Disease Control Division, Ministry of Health; 2011.

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

D In patients with hyperglycaemic crisis, diabetes mellitus can be diagnosed without further testing (pg 42).

Grade D, Level 4

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 plasma glucose ≥11.1 mmol/l

Other individuals should have a repeat test on a subsequent day (pg 42).

Grade B, Level 2^{++}

D When two different tests are available for the same patient and the results for both tests are above the diagnostic thresholds, the diagnosis of diabetes is confirmed (pg 42).

Grade D, Level 4

D When two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point (usually the fasting plasma glucose or 2-hour post-challenge glucose) should be repeated (pg 42).

Grade D, Level 4

D Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus (pg 43).

Grade D, Level 4

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 43).

Grade B, Level 2^{++}

D If a second test fails to confirm the diagnosis, barring a laboratory error, such patients are likely to have test results near the margins of the threshold for a diagnosis. The healthcare professional might opt to follow the patient closely and repeat the testing in 6-12 months (pg 43).

Grade D, Level 4

GPP HbA_{1c} is not recommended as a screening and diagnostic tool for diabetes mellitus until its performance in our multi-ethnic population has been evaluated (pg 43).

GPP

B Intermediate states of glucose metabolism termed impaired fasting glucose and impaired glucose tolerance should be recognised as defined in Table 1 (pg 46).

Grade B, Level 2^{++}

D Screening should be considered in adults of any age who have one or more risk factors for diabetes. In those without risk factors, testing should begin at 40 years (pg 47).

Grade D, Level 4

D 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) (pg 47).

Grade D, Level 4

Lifestyle modification

D Individuals who have diabetes should receive individualised medical nutritional therapy as needed to achieve treatment goals, preferably provided by a dietitian familiar with the components of diabetes medical nutrition therapy (pg 49).

Grade D, Level 4

GPP Special attention should be paid to the diabetic patient's dietary requirements during periods of sickness, fasting, travel and exercise (pg 49).

GPP

D A diet for diabetes should contain a good balance of carbohydrate, protein and fat, adjusted to meet the individual's metabolic goals and preferences (pg 50).

Grade D, Level 4

D Individualised meal planning for diabetes should include optimisation of food choices to meet recommended dietary allowance for all micronutrients, providing adequate vitamins and minerals (pg 50).

Grade D, Level 4

B Meal and snack carbohydrate intake for diabetes should be consistently distributed throughout the day, on a day to day basis, as consistency in carbohydrate intake has been shown to result in improved glycaemic control (pg 50).

Grade B, Level 2+

D Consumption of macronutrients is based on recommended dietary allowance (RDA) for healthy eating; 50-60% of total energy from carbohydrates should be encouraged (pg 50).

Grade D, Level 4

B If weight reduction is needed, it should be attempted gradually (0.25 to 1.0 kg/week). In overweight or obese patients with type 2 diabetes, a weight loss of 5-10% of body weight achieved through lifestyle interventions is a realistic goal (pg 51).

Grade B, Level 2+

D Dietary protein intake of approximately 15-20% of daily energy intake is appropriate for most patients with type 2 diabetes (pg 51).

Grade D, Level 4

D It is recommended that total calories from fat intake be kept to <30% of total calorie intake in diabetic patients (pg 51).

Grade D, Level 4

D Trans fats should be limited to 1% of total energy intake and cholesterol intake (<200 mg daily) to reduce risk for cardiovascular disease. These goals are similar for individuals with pre-existing cardiovascular disease (pg 52).

Grade D, Level 4

B Recommendations for fibre intake for people with diabetes are similar to the recommendation for the general population. A daily consumption of a diet containing 20-35 g of dietary fibre from a wide variety of food sources is recommended (pg 52).

Grade B, Level 2+

D Sodium intake should be restricted to <2 g per day for diabetic individuals with hypertension (pg 52).

Grade D, Level 4

D Diabetes patients with poor glycaemic control or are overweight should abstain from alcohol. If individuals choose to drink, intake should be limited to a moderate amount, as per the general population (no more than two drinks for women per day and no more than three drinks per day for men) (pg 52).

Grade D, Level 4

B Individuals who choose to use non-nutritive sweeteners should be advised that some of these products might contain energy and carbohydrate from sources that might need to be accounted for (pg 52).

Grade B, Level 2+

D For exercise more vigorous than brisk walking, a pre-exercise physician evaluation is recommended for individuals with diabetes to identify cardiovascular risks and any complications of severe neuropathy or severe diabetic retinopathy that may contraindicate certain activities and predispose to injury (pg 53).

Grade D, Level 4

D Individuals with severe proliferative diabetic retinopathy should avoid activities that greatly increase intraocular pressure and risk of haemorrhage (pg 54).

Grade D, Level 3

B Individuals with peripheral neuropathy and without acute ulceration may participate in moderate weight-bearing exercise. Comprehensive foot care, use of appropriate footwear and daily foot check is recommended (pg 54).

Grade B, Level 2+

B Individuals with type 2 diabetes should undertake at least 150 mins/ week of moderate to vigorous aerobic exercise spread out during at least 3 days of the week, with no more than 2 consecutive days between bouts of exercise (pg 54).

Grade B, Level 1+

D Individuals with diabetes, especially those on insulin treatment or secretagogues, may require medication dose adjustments and should receive specific education on the prevention of exercise induced hypoglycaemia (pg 55).

Grade D, Level 4

C Individuals with diabetes should be encouraged to stop smoking (pg 55).

Grade C, Level 3

B People with diabetes should receive Diabetes Self-Management Education (DSME) when their diabetes is diagnosed and as needed thereafter (pg 57).

Grade B, Level 2+

D Assessment of psychological and social wellbeing should be included as an ongoing part of diabetes management (pg 59).

Grade D, Level 4

D Clinicians should provide the following psychosocial support to patients during the diagnosis phase of diabetes management:

- Provide medical information and psychological support.
- Be accessible and sensitive to patient's needs.
- Provide information and repeat if necessary as they may not retain much at this stage.
- Introduce to other patients to get them support and an accepting environment
- Involve other family members if necessary

(pg 59) **Grade D, Level 4**

D Clinicians should provide the following psychosocial support to patients during the maintenance phase of diabetes management:

- Motivate patient and family to maintain optimal control

- Create an individualised workable regimen and help patient adhere to it
- Ensure good support from diabetes team
- Check for signs of diabetes burnout
- Consider educational intervention
- Follow up and review behavioural changes
- Modify treatment if necessary

(pg 60) **Grade D, Level 4**

D Clinicians should provide the following psychosocial support to patients during the complications phase of diabetes management:

- Giving them the space to vent and providing them with a lot of realistic reassurance is important
- Do not overwhelm with information but allow for grieving first
- Gentle motivation to encourage patients to maintain adherence to treatment regimen and possibly revising some of the information or education will be helpful
- Counselling is important but needs to be timely

(pg 60) **Grade D, Level 4**

D Patients with diabetes should be encouraged to find support from other persons and families living with diabetes and community programmes which reinforces diabetes education and promotes living well with diabetes. These community based programmes provide a safe and accepting environment for learning and sharing with others who live with the same condition (pg 60).

Grade D, Level 4

Pharmacotherapy

B Long-acting sulphonylureas e.g., chlorpropamide and glibenclamide, carry a high risk of hypoglycaemia and are not recommended (pg 62).

Grade B, Level 2^{++}

A Patients with type 2 diabetes may initially be treated with lifestyle modification (diet and exercise) unless they are symptomatic or severely hyperglycaemic (i.e. random blood glucose >15 mmol/l or fasting blood glucose >10 mmol/l) – in which case pharmacological therapy should be initiated together with lifestyle intervention (pg 63).

Grade A, Level 1^{+}

A Oral glucose lowering agents should be started if glycaemic targets are not achieved in a timely and appropriate manner (pg 63).

Grade A, Level 1+

A 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 (pg 63).

Grade A, Level 1+

A Insulin therapy should be considered, 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 63).

Grade A, Level 1+

A Metformin is usually considered first-line pharmacotherapy, and sulphonylureas / dipeptidyl peptidase 4 (DPP-IV) inhibitors / alpha-glucosidase inhibitors are reasonable alternatives as first-line pharmacotherapy (pg 64).

Grade A, Level 1+

A For type 2 diabetes, two or more oral agents, or insulin therapy, either alone or in combination with oral agents, may be required (pg 64).

Grade A, Level 1+

A For type 2 diabetes, other oral agents are acceptable alternatives to metformin as initial monotherapy, if the person does not tolerate metformin, or where metformin is contraindicated (pg 64).

Grade A, Level 1+

A In the setting of severely uncontrolled type 2 diabetes (for example, HbA_{1c} >10%, random glucose levels consistently above 16.7mmol/L), the presence of ketonuria, or symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy in combination with lifestyle intervention may be the initial treatment of choice (pg 64).

Grade A, Level 1+

D In elderly patients, initiating therapy with low-dose, short-acting oral glucose lowering agents is recommended (pg 65).

Grade D, Level 4

D Metformin is usually contraindicated in the presence of severe renal or hepatic insufficiency as it may be associated with lactic acidosis (pg 65).

Grade D, Level 4

D It is advisable to use metformin with caution in those at risk of a sudden deterioration in renal function and those with eGFR <45ml/min/1.73m^2 and to cease metformin usage if the eGFR is below 30ml/min/1.73m^2 (pg 65).

Grade D, Level 4

D Metformin must be used with care in the presence of co-morbid conditions which increase the risk of lactic acidosis (e.g., class III or IV cardiac failure) (pg 66).

Grade D, Level 4

D Thiazolidinediones (in particular, rosiglitazone) are contraindicated in patients with acute coronary syndrome, ischaemic heart disease, and all classes of heart failure (including New York Heart Association (NYHA) Functional Classification Class I/II heart failure patients) and are also not recommended for use in patients with peripheral arterial disease (pg 66).

Grade D, Level 4

GPP Treatment choices should be individualised and culturally appropriate, and patients should have the opportunity to make informed decisions on their care and treatment options, in partnership with their healthcare providers (pg 67).

GPP

D The use of exenatide is not recommended in type 2 diabetes patients with a history of pancreatitis (pg 68).

Grade D, Level 4

A All patients with type 1 diabetes 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 68).

Grade A, Level 1^{+}

D 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, matching of insulin dose and carbohydrate intake, and dose adjustments during sick days, travel, exercise, and changes in food intake (pg 68).

Grade D, Level 4

B Insulin therapy should be managed with relevant and regular insulin and hypoglycaemia-related self-management training with the common goal of improved glycaemic control and reduction in risk of severe hypoglycaemia (pg 69).

Grade B, Level 2^{++}

D In type 2 diabetes, introduction of insulin should not be delayed if metabolic control becomes suboptimal. This may be initiated as a bedtime dose of intermediate-acting or long-acting insulin with maintenance of oral agents during the day (pg 75).

Grade D, Level 4

D When glycaemic control is not achieved despite the addition of basal insulin to oral agents, discontinuing sulphonylureas and switching to premixed twice daily or basal-bolus insulin regimens becomes necessary. However, metformin and α-glucosidase inhibitors 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. Patients with type 2 diabetes who are switched to insulin therapy 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 (pg 75).

Grade D, Level 4

Glycaemic control: assessment and targets

B Self-monitoring of blood glucose is recommended for patients with type 1 or type 2 diabetes who are using insulin (pg 77).

Grade B, Level 2++

D Self-monitoring of blood glucose should be considered in the following groups of patients with type 2 diabetes who are not treated with insulin:

- those at increased risk of developing hypoglycaemia or its consequences (e.g., patients who are using sulphonylureas)
- those pregnant patients with pre-existing diabetes or gestational diabetes
- those experiencing acute illness
- those who have failed to achieve glycaemic goals
- those undergoing fasting, for example, during Ramadan

(pg 78) **Grade D, Level 4**

B Self-monitoring of blood glucose should be carried out 3 or more times daily for patients with type 1 diabetes (pg 79).

Grade B, Level 2++

GPP For patients with unstable metabolic control, changes in daily routine, alterations of treatment regimens or acute illness, the frequency of self-monitoring of blood glucose should be increased (pg 79).

GPP

GPP Healthcare professionals should be familiar with the practical use of glucometers (pg 79).

GPP

B To ensure optimal benefit from self-monitoring of blood glucose, patients must be educated on the interpretation of glucose levels (pg 80).

Grade B, Level 1+

GPP 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 (pg 80).

GPP

GPP It is recommended that calibration checks of meters are periodically conducted using standard solutions according to the manufacturer's recommendations (pg 80).

GPP

D Continuous glucose monitoring (CGM) may be used as a supplemental tool to SMBG in patients with hypoglycaemia unawareness and/or frequent hypoglycaemic episodes (pg 81).

Grade D, Level 3

B Self-monitoring of urine glucose is not recommended for monitoring of glycaemic status (pg 81).

Grade B, Level 1+

A Ketone monitoring should be performed during sustained hyperglycaemia (e.g., blood glucose > 14.0 mmol/l) in patients with type 1 diabetes, especially during acute illness. Blood ketone monitoring is preferable to urine ketone monitoring (pg 81).

Grade A, Level 1+

D Glycated haemoglobin (HbA_{1c}) should be performed routinely in all patients with diabetes, at initial assessment and then as part of follow-up care (pg 82).

Grade D, Level 4

D The measurement of HbA_{1c} should be done in laboratories that utilise DCCT-aligned assays (DCCT - Diabetes Control and Complications Trial) (pg 83).

Grade D, Level 4

D The following schedule is recommended for HbA_{1c} testing in patients with diabetes:

- 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 83).

Grade D, Level 4

B HbA_{1c} result should be made available at the time that the patient with diabetes is seen (pg 83).

Grade B, Level 2^{++}

D The targets of glycaemic control should be individualised (pg 83).

Grade D, Level 4

GPP Patients should participate in the process of defining their targets of glycaemic control (See Table 6) (pg 84).

GPP

A The HbA_{1c} target for most non-pregnant adults with type 1 or type 2 diabetes should be ≤7.0% or ≤ 53 mmol/mol (pg 84).

Grade A, Level 1^{++}

B Lowering HbA_{1c} target to ≤6.5% or ≤ 47.5 mmol/mol may be considered for some patients with type 2 diabetes at doctor and patient judgement, if this can be achieved without significant hypoglycaemia. Such patients include those with short duration of diabetes, long life expectancy and no significant cardiovascular disease (pg 85).

Grade B, Level 1^{+}

D Less stringent HbA_{1c} target (e.g., 7.0 to 8.5% or 53 mmol/mol to 69.4 mmol/mol) may be adopted for some patients vulnerable to the harmful effects associated with tight glycaemic control. Such patients include those with very long duration of diabetes, known history of severe hypoglycaemia, advanced atherosclerosis and advanced age (pg 86).

Grade D, Level 4

GPP Doctors should be vigilant in preventing hypoglycaemia by reviewing treatment regimens in patients with near-normal HbA_{1c} levels (e.g., <6.0% or 42.1 mmol/mol), especially those treated with insulin or insulin secretagogues (pg 86).

GPP

Prevention of cardiovascular disease in people with diabetes

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

History – which should include:

- Smoking
- Hypertension
- Pre-existing cardiovascular disease (including angina, myocardial infarction, stroke, PAD)
- Family history of premature coronary artery disease (non-modifiable)

Physical examination – which should include:

- Assessment for peripheral vascular disease
- Measurement of blood pressure at every visit

Tests – which should include:

- Fasting serum lipids at or soon after diagnosis and at least annually
- Urine microalbumin or protein at least annually
- Serum creatinine and estimation of eGFR (See chapter 8)
- Electrocardiogram (resting) routinely at baseline. Subsequent ECG may be performed when clinically indicated

(pg 88) **GPP**

B For patients with type 2 diabetes mellitus who have hypertension, an acceptable treatment-initiation and target blood pressure is <140/80 mm Hg (pg 91).

Grade B, Level 2+

B An angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) should be included as part of antihypertensive regimen for people with type 2 diabetes requiring pharmacotherapy for hypertension, unless not well tolerated (pg 93).

Grade B, Level 2+

D All persons with type 2 diabetes mellitus should have a full lipid profile, including low density lipoprotein (LDL) cholesterol, fasting triglyceride and high density lipoprotein (HDL) cholesterol, measured at the time of diagnosis. These should be obtained after 10-12 hours of fasting (pg 96).

Grade D, Level 4

D If optimal, serum lipids should be measured 12-monthly in persons with type 2 diabetes (pg 96).

Grade D, Level 4

D The majority of patients with type 2 diabetes mellitus should have a primary low density lipoprotein (LDL) cholesterol goal <2.6 mmol/L and should receive medical nutrition and pharmacological therapy to achieve this goal (pg 96).

Grade D, Level 4

D Patients with diabetes who have overt cardiovascular disease and / or chronic kidney disease but are not on maintenance hemodialysis should have low density lipoprotein (LDL) cholesterol lowered with combination of dietary and pharmacological means to a target of <2.1 mmol/L (pg 96).

Grade D, Level 4

D When making a therapeutic decision with the patient, the potential benefits of adding/increasing lipid-lowering pharmacological treatment, needs to be considered together with the potential risks of such treatment (pg 96).

Grade D, Level 4

D For most patients with type 2 diabetes mellitus where low density lipoprotein (LDL) cholesterol is >2.6 mmol/L, an HMG CoA reductase inhibitor (statin) should be started concurrently with therapeutic lifestyle modification (pg 97).

Grade D, Level 4

D It is reasonable to initiate low dose aspirin for primary prevention in people with diabetes and no previous history of vascular disease at age 50 years for men, and 60 years for women, provided they also have at least one more of the following cardiovascular risk factors: smoking, hypertension, dyslipidaemia, family history of premature cardiovascular disease and albuminuria (pg 99).

Grade D, Level 4

GPP 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 (pg 99).

GPP

Diabetic nephropathy – screening and treatment

D It is recommended to perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of 5 years and in all type 2 diabetic patients, starting at diagnosis (pg 101).

Grade D, Level 4

D Measure serum creatinine at least annually in all adults with diabetes (regardless of the degree of urine albumin excretion) is recommended. The serum creatinine should be used to estimate glomerular filtration rate (GFR) and stage the level of chronic kidney disease (CKD), if present (pg 102).

Grade D, Level 4

C It is only recommended to estimate renal function with the Modification of Diet in Renal Disease (MDRD) equation when eGFR is below 60 mls/min/1.73m^2 (pg 103).

Grade C, Level 2$^+$

A To reduce the risk or slow the progression of nephropathy, optimised glucose control is recommended (pg 104).

Grade A, Level 1$^+$

A To reduce the risk or slow the progression of nephropathy, optimised blood pressure control is recommended (pg 104).

Grade A, Level 1$^+$

A It is recommended that in the treatment of the non-pregnant patient with micro- or macroalbuminuria, either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be used (pg 105).

Grade A, Level 1+

A In patients with type 1 diabetes, with hypertension and any degree of albuminuria, angiotensin-converting enzyme (ACE) inhibitors are recommended (pg 105).

Grade A, Level 1+

A In patients with type 2 diabetes, hypertension, and microalbuminuria, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended (pg 105).

Grade A, Level 1+

A In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), angiotensin receptor blockers (ARBs) are recommended (pg 105).

Grade A, Level 1+

D In patients with diabetes, if one class [either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)] is not tolerated, the other should be substituted (pg 105).

Grade D, Level 4

D When angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or diuretics are used, it is recommended to monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia (pg 106).

Grade D, Level 4

A To reduce the risk or slow the progression of nephropathy, optimised lipid control is recommended (pg 106).

Grade A, Level 1+

A Reduction of protein intake to 0.8–1.0 g per kg body wt per day in individuals with diabetes and earlier stages of chronic kidney disease (CKD) and to 0.8 g per kg body wt per day in the later stages of CKD is recommended to improve measures of renal function (urine albumin excretion rate, GFR) (pg 107).

Grade A, Level 1+

A It is recommended to consider a low-dose aspirin in diabetic individuals with a history of vascular disease (pg 107).

Grade A, Level 1+

D It is recommended to consider low-dose aspirin in diabetic individuals who carry significant cardiovascular risk burden (pg 107).

Grade D, Level 4

D Continual monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended for both type 1 and type 2 diabetes patients (pg 108).

Grade D, Level 4

D It is recommended that when estimated GFR (eGFR) is <60 ml.min/1.73 m^2, evaluate and manage potential complications of Chronic Kidney Disease (CKD) (pg 108).

Grade D, Level 4

D It is recommended to consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease (pg 108).

Grade D, Level 4

Prevention and management of eye complications

D 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 110).

Grade D, Level 4

D Retinal screening preferably using retinal photography or direct ophthalmoscopy (if retinal photography is not available) through dilated pupils is recommended (pg 110).

Grade D, Level 4

D Type 1 diabetic patients should have an eye examination 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 111).

Grade D, Level 4

D Women with diabetes mellitus who intend to have children should preferably have an eye examination prior to conception, followed by one during the early first trimester. Further eye examinations during pregnancy may be done depending on the results of the first trimester examination (pg 111).

Grade D, Level 4

A Good glycaemic control (HbA_{1c} preferably 6.5 to 7.5% or 47.5 to 58.5 mmol/mol) should be instituted to reduce the risk and progression of diabetic retinopathy (pg 113).

Grade A, Level 1+

D Rapid normalisation of blood glucose may worsen retinopathy and thus retinal assessment should be carried out before initiation of intensive insulin therapy and then at 3-monthly intervals for 6-12 months. Patients should be carefully monitored during this period (pg 114).

Grade D, Level 3

A Good control of blood pressure at or below 130/80 mmHg should be instituted to reduce the risk and progression of diabetic retinopathy (pg 114).

Grade A, Level 1+

B Significant hyperlipidaemia should be treated to retard diabetic retinopathy. Consideration should be given to using fenofibrate (pg 115).

Grade B, Level 1+

GPP Diabetic patients found to have diabetic macular oedema or moderate and more severe non- retinopathy by their physicians should be referred for further ophthalmological assessment (pg 117).

GPP

A Timely laser therapy should be offered to patients with proliferative diabetic retinopathy and diabetic macular oedema (pg 118).

Grade A, Level 1+

GPP Diabetic patients with visual acuity of 6/18 or worse or with diabetic macular oedema should be referred for further ophthalmological assessment (pg 118).

GPP

A Pan-retinal laser photocoagulation should be instituted for severe and proliferative diabetic retinopathy as it produces a 50% reduction in risk for severe visual loss and need for vitrectomy (pg 119).

Grade A, Level 1+

A Focal/grid laser photocoagulation should be instituted for diabetic macular oedema as it results in a 50% reduction in risk for moderate visual loss (pg 119).

Grade A, Level 1+

A Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents may be offered to patients with diabetic macular oedema, particularly in cases where laser photocoagulation has not been effective (pg 120).

Grade A, Level 1+

B Vitrectomy may be offered to selected patients with advanced diabetic retinopathy (pg 121).

Grade B, Level 1+

Prevention of diabetic foot complications

B All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions (pg 124).

Grade B, Level 2+

B The assessment of the feet involves risk identification, treatment and patient education appropriate to the level of risk (pg 124).

Grade B, Level 2+

GPP All patients, regardless of risk category, should receive ongoing education on footcare and footwear advice (pg 124).

GPP

C Patients identified with foot-related risk conditions should have access to a specialised footcare team which should include diabetes specialist, podiatrist, physiotherapist trained in diabetes, diabetes nurse educator, vascular and orthopaedic surgeons (pg 126).

Grade C, Level 3

GPP Urgent referral to a specialised footcare team is needed in the presence of ulcerations, severe foot infection and gangrene (pg 128).

GPP

Management of women with pre-gestational and gestational diabetes mellitus

B All women with diabetes in the reproductive age group should receive prepregnancy counselling, particularly before starting a family (pg 132).

Grade B, Level 1-

GPP Wherever possible, prepregnancy counselling should be performed jointly by a multi-disciplinary team skilled in diabetes care, including the physician, obstetrician, dietician, nurse-educator and other specialists (pg 133).

GPP

D Risk assessment for gestational diabetes should be undertaken at the first antenatal visit (pg 133).

Grade D, Level 4

B Women at high-risk for gestational diabetes (GDM) should undergo an oral glucose tolerance test (OGTT) as early in pregnancy as feasible. Re-evaluation should be performed at 24–28 weeks of gestation if glucose intolerance is not present at the early screen (pg 134).

Grade B, Level 1+

D In pregnant women who are not at high risk for gestational diabetes, 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 135).

Grade D, Level 3

B Gestational diabetes is diagnosed with a 75 g oral glucose tolerance test (OGTT). A fasting venous plasma glucose ≥7.0 mmol/l or a 2-hour venous plasma glucose of ≥7.8 mmol/l is diagnostic of gestational diabetes. Casual venous plasma levels ≥11.1 mmol/l on 2 successive occasions would confirm gestational diabetes without recourse to oral glucose tolerance testing (pg 135).

Grade B, Level 1

D All women diagnosed with pregestational diabetes and those diagnosed with gestational diabetes should receive specialised care (pg 135).

Grade D, Level 3

B In gestational diabetes, dietary control should be used in the first instance to attain glycaemic goals. Sweet foods should be avoided and caloric intake reduced if the woman is overweight or obese. The diet should contain more complex carbohydrates, more fibre, and less saturated fat. Nutritional counselling should be individualised, taking into account the patient's body weight, weight gain and physical activity (pg 136).

Grade B, Level 2^{++}

B If nutritional therapy does not consistently maintain a fasting or pre-meal capillary blood glucose of <5.5 mmol/l and/or a 1-hour postprandial capillary glucose of <7.8 mmol/l 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 136).

Grade B, Level 2^{++}

C In pregestational diabetes, individualised intensive (multi-dose) insulin therapy is often necessary to achieve and maintain target blood glucose levels (pg 137).

Grade C, Level 2+

D Maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting or pre-meal state, and/or <7.8 mmol/l one hour after meals, or <6.7 mmol/l two hours after meals (pg 137).

Grade D, Level 4

D Self-monitoring of blood glucose (SMBG) is essential during pregnancy for women with gestational diabetes and pregestational diabetes. Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycaemic targets (pg 137).

Grade D, Level 3

D Women with pregestational type 1 diabetes should be advised to test for ketonuria or ketonaemia if they become hyperglycaemic or unwell (pg 137).

Grade D, Level 4

D Oral glucose-lowering drugs are not recommended during pregnancy under normal circumstances. Women with pregestational type 2 diabetes who become pregnant while taking oral glucose-lowering drugs should be switched to insulin therapy (pg 138).

Grade D, Level 4

D An early pregnancy scan should be performed to confirm viability and accurately date the pregnancy in women with pregestational diabetes, especially when glycaemic control is suboptimal or changes in medications are required (pg 138).

Grade D, Level 4

B A detailed foetal anomaly scan, including four-chamber cardiac view and outflow tracts, should be performed between 18–22 weeks in women with pregestational diabetes or when overt diabetes is diagnosed in the early pregnancy (pg 138).

Grade B, Level 2++

D Women with pregestational diabetes and gestational diabetes should be offered ultrasound monitoring of foetal growth (foetal abdominal circumference and/or estimated foetal weight) and amniotic fluid volume every 4 weeks from 28 to 36 weeks (pg 139).

Grade D, Level 4

D Mothers with gestational diabetes mellitus and pregestational diabetes should be taught to monitor foetal movements during the last 10–12 weeks of pregnancy and to report immediately any reduction in the perception of foetal movements (pg 139).

Grade D, Level 4

C 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 (pg 139).

Grade C, Level 2^{+}

C In women with gestational diabetes mellitus as well as those with pregestational diabetes, the measurement of blood pressure and dipstick testing for urinary protein is recommended at each antenatal visit to detect the development of pregnancy-induced hypertension and pre-eclampsia, especially if there is pre-existing nephropathy (pg 139).

Grade C, Level 2^{+}

GPP Women with pregestational diabetes should have their serum creatinine and electrolytes assessed at the first antenatal visit and in the third trimester (pg 139).

GPP

B For women with pregestational diabetes, a retinal assessment should be performed as soon as possible after the first antenatal visit if it has not been done in the preceding 12 months. If any diabetic retinopathy is present, an additional assessment should be performed at 16–20 weeks of gestation. If the first assessment is normal, an assessment should be repeated at 28 weeks of gestation (pg 140).

Grade B, Level 2^{++}

GPP More frequent assessment may be required in women with poor glycaemic control, hypertension and/or pre-existing retinopathy (pg 140).

GPP

D Women with insulin-treated pregestational diabetes or gestational diabetes mellitus who are receiving corticosteroids for foetal lung maturation should receive additional insulin treatment and close monitoring of glucose levels (pg 140).

Grade D, Level 4

B Betamimetic drugs (e.g., salbutamol) should not be used for tocolysis in women with diabetes as they may lead to significant hyperglycaemia (pg 140).

Grade B, Level 2^{++}

D Delivery should be at term for women with pregestational diabetes and gestational diabetes mellitus unless specific obstetric or medical factors dictate otherwise (e.g., foetal macrosomia, poor glycaemic control, polyhydramnios, pre-eclampsia, intrauterine growth restriction) (pg 140).

Grade D, Level 4

D Vaginal delivery is preferable unless there is an obstetric or medical contraindication. The presence of diabetes should not itself constitute an indication for elective caesarean delivery (pg 141).

Grade D, Level 4

D During labour and birth, capillary blood glucose should be monitored every 1–4 hours in women with pregestational diabetes and gestational diabetes mellitus and maintained at 4–7 mmol/l (pg 141).

Grade D, Level 4

D Intravenous dextrose and insulin infusion is recommended during labour and birth for women whose blood glucose is not maintained at 4–7 mmol/l (pg 141).

Grade D, Level 4

D Women with pregestational type 1 diabetes should be considered for intravenous dextrose and insulin infusion from the onset of established labour (pg 141).

Grade D, Level 4

D The neonatologist should be informed of deliveries of infants of women with diabetes so that possible complications like neonatal hypoglycaemia may be monitored and treated early (pg 141).

Grade D, Level 4

C Screening for abnormalities should also be performed in infants of woman with diabetes soon after birth (pg 141).

Grade C, Level 2+

D Babies of women with diabetes should be fed as soon as possible after birth (within 30 minutes) (pg 141).

Grade D, Level 4

D Infants of women with diabetes who present with clinical signs of hypoglycaemia should have their blood glucose tested and be treated with intravenous dextrose as soon as possible. Close monitoring of blood glucose levels is necessary within the first 48 hours of the baby's life (page 141).

Grade D, Level 4

D 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 (page 142).

Grade D, Level 4

D Women with gestational diabetes should discontinue glucose-lowering treatment immediately after birth and monitor their blood glucose levels (pg 142).

Grade D, Level 4

D Women with insulin-treated pregestational diabetes should reduce their insulin doses immediately after birth and monitor their blood glucose levels carefully to establish the appropriate dose (pg 142).

Grade D, Level 4

GPP Women who are treated with insulin post-delivery should be informed that they are at increased risk of hypoglycaemia in the postnatal period, especially when breastfeeding, and should be advised to have a meal or snack available before or during feeds (pg 142).

GPP

D Breastfeeding is recommended for infants of women with diabetes (pg 142).

Grade D, Level 3

GPP Insulin is recommended for glycaemic control in women with diabetes who breastfeed (pg 142).

GPP

GPP Women with pregestational diabetes who are breastfeeding should continue to avoid any drugs for the treatment of diabetes complications that were discontinued for safety reasons in the pre-conception period (pg 143).

GPP

B All subsequent pregnancies in women with gestational diabetes carry a risk for gestational diabetes mellitus. Early evaluation of glucose tolerance in future pregnancies should be stressed (pg 143).

Grade B, Level 2^{++}

D Women with a history of gestational diabetes mellitus should be offered lifestyle advice aimed at diet modification, weight control and increasing physical activity to reduce their risk of subsequent development of diabetes (pg 143).

Grade D, Level 4

C For women with gestational diabetes, a 75 g 2-h oral glucose tolerance test (OGTT) should be performed 6–12 weeks postpartum and the woman reclassified and counselled according to criteria accepted in the non-pregnant state (pg 143).

Grade C, Level 2^{+}

D Women with a history of gestational diabetes should have lifelong screening for the development of prediabetes or diabetes at least once every 3 years (pg 144).

Grade D, Level 4

D In women with prediabetes or overt diabetes, 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/or other risk factors for vascular disease. Progestin-only preparations may be suitable for these women (pg 144).

Grade D, Level 3

D Low-dose oestrogen-progestin oral contraceptives and intrauterine devices are not contraindicated in women with previous gestational diabetes (pg 144).

Grade D, Level 3

D Oestrogen-progestogen contraceptives should be avoided in women with complications of diabetes and/or other risk factors for vascular disease (pg 144).

Grade D, Level 3

Management of the child and adolescent with diabetes mellitus

GPP Children and adolescents with suspected diabetes should be referred to a specialist for early assessment, where possible, on the same day (pg 145).

GPP

B Children and adolescents with either type 1 diabetes or type 2 diabetes should be provided ongoing and structured diabetes care by a multi-disciplinary diabetes care team (pg 146).

Grade B, Level 2^{++}

GPP Diabetes education should involve the family and child to include learning about blood glucose monitoring, insulin administration, hypoglycaemia and sick day management. As the child matures, diabetes education should emphasise self-care responsibilities shifting from the parent to child, under parental guidance and supervision (pg 146).

GPP

D Include psycho-educational intervention strategies and planned transition in the management of adolescents with diabetes (pg 147).

Grade D, Level 4

GPP Blood glucose targets should be individually determined with a goal to achieving a value as close to normal as possible as there is little age-related scientific evidence for strict glucose targets (pg 148).

GPP

A Children and adolescents with type 1 diabetes mellitus or type 2 diabetes mellitus, and their families should be informed that the target for long term blood glucose control is a HbA_{1c} level of less than 7.5% or 58.5 mmol/mol without frequent hypoglycaemia (pg 148).

Grade A, Level 1^+

A Children and adolescents with type 1 diabetes should be encouraged to use blood glucose measurements for monitoring of glycaemic control because it is associated with reduced levels of HbA_{1c} (pg 148).

Grade A, Level 1^+

GPP Consider the possibility of antecedent nocturnal hypoglycaemia if fasting blood glucose is <4mmol/l (pg 148).

GPP

C Screening for type 2 diabetes in asymptomatic children and adolescents is not recommended as a public health strategy (pg 149).

Grade C, Level 2^+

GPP Type 1 diabetes mellitus in children and adolescents should be managed by an endocrinologist or physician with a special interest in childhood diabetes (pg 149).

GPP

C Self-monitoring of blood glucose is an essential tool in the optimal management of childhood and adolescent type 1 diabetes mellitus and should be must be used in conjunction with insulin treatment (pg 150).

Grade C, Level 2^+

C Children and adolescents with type 1 diabetes mellitus should be offered screening for:

- Thyroid disease at diagnosis and annually thereafter.
- Retinopathy annually from the age of 12 years.
- Microalbuminuria annually from the age of 12 years

(pg 150). **Grade C, Level 2+**

C Children with type 2 diabetes mellitus may initially be treated with lifestyle modification (diet and exercise), unless they are symptomatic or severely hyperglycaemic (pg 151).

Grade C, Level 2+

C Lifestyle changes in diet and exercise should be recommended for all children with type 2 diabetes mellitus and continued, even after addition of pharmacologic therapy (pg 152).

Grade C, Level 2+

C Metformin may be started as the first-line oral agent in children with type 2 diabetes mellitus if blood glucose targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control (pg 152).

Grade C, Level 2+

A 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 (pg 152).

Grade A, Level 1+

A If monotherapy with metformin over 3-6 months has failed, insulin should be added to the treatment (pg 152).

Grade A, Level 1+

C Children and adolescents with type 2 diabetes mellitus should be offered co-morbidity screening for:

- Albuminuria at diagnosis and annually thereafter.
- Hypertension at diagnosis and annually thereafter.
- Dyslipidaemia soon after diagnosis and annually thereafter (pg 153).

Grade C, Level 2+

GPP Albuminuria should be evaluated at diagnosis and blood pressure should be evaluated at every visit. Confirmed hypertension (BP>95% for age, gender and height) or albuminuria can be treated with an angiotensin-converting enzyme (ACE) inhibitor (pg 153).

GPP

GPP Pharmacotherapy is warranted if low density lipoprotein remains elevated (≥3.4mmol/l) after 6 months of optimised glucose control and diet. Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention, although long term safety data are not available (pg 153).

GPP

GPP Evaluation for non-alcoholic fatty liver disease (NAFLD) and inquiries about puberty, menstrual irregularities and obstructive sleep apnea should be done at diagnosis and annually thereafter (pg 153).

GPP

Diagnosis and management of the adult with type 1 diabetes mellitus

GPP Patients who are suspected to have type 1 diabetes should be referred to the specialist promptly for assessment (pg 154).

GPP

GPP Individuals with type 1 diabetes should have access to a multi-disciplinary team consisting of an endocrinologist, a nurse educator, a dietitian and a mental health professional qualified to provide up to date education and support (pg 155).

GPP

A Most people with type 1 diabetes should be treated with multiple dose insulin (MDI) injections (at least three injections per day of prandial insulin and at least one injection per day of basal insulin) or continuous subcutaneous insulin infusion (CSII) (pg 155).

Grade A, Level 1+

A Most people with type 1 diabetes should use insulin analogues to reduce the risk of hypoglycaemia (pg 155).

Grade A, Level 1+

A Individuals using rapid-acting insulin by injection or insulin pump should adjust the meal and snack insulin doses based on the carbohydrate content of the meals and snacks (pg 155).

Grade A, Level 1+

B People with diabetes should receive diabetes self-management education and ongoing support (pg 156).

Grade B, Level 2+

C Screening of psychosocial functioning, especially anxiety and depression should be performed. Those with positive screening should be referred promptly for treatment (pg 157).

Grade C, Level 2+

GPP Patients with type 1 diabetes should have thyroid function checked every 1-2 years (pg 157).

GPP

Prevention of type 2 diabetes mellitus

B Screening for asymptomatic individuals for type 2 diabetes mellitus should be carried out on an opportunistic basis. Testing should be considered in adults of any age who have one or more risk factors for diabetes. In those without risk factors, testing should begin at 40 years (pg 159).

Grade B, Level 2++

A Lifestyle changes with modest weight loss (5-10% of body weight) and moderate intensity physical activity (~30 minutes daily) is the treatment of choice with individuals with impaired fasting glucose / impaired glucose tolerance (pg 161).

Grade A, Level 1^{++}

B Metformin may be considered for the very high risk individual (please refer to chapter on Diagnosis and screening) with impaired fasting glucose / impaired glucose tolerance of age < 60 and BMI ≥ $35kg/m^2$ (pg 162).

Grade B, Level 2^{++}

Clinical quality improvement

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 166).

Grade A, Level 1^{+}

GPP Data to measure the outcomes of diabetes management should be obtained from the individual with diabetes (pg 166).

GPP

1 Introduction

1.1 Objectives and scope of guideline

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 Target group

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 Guideline development

These guidelines have been produced by a committee of endocrinologists, family practitioners and primary care specialists, ophthalmologist, dietitian, social worker, and patient representative, appointed by the Ministry of Health. They were developed by the adaptation of existing guidelines, by the review of relevant literature and by expert clinical consensus with consideration of local practice. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

1.4 What's new in the revised guidelines

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

- In Chapter 3, we have explained the rationale for criteria in diagnosing diabetes. In particular, for asymptomatic patients with a first test that meets criteria, we have attempted to provide more clarity on how to choose a second test, and how to interpret the findings.

- Chapter 4 is a new chapter which brings emphasis to two areas contributing towards positive outcomes in diabetes care: diabetes self-management education, and psychosocial assessment and holistic care of the person with diabetes.

- 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 pharmacological agents.

- Chapter 6 focuses on glycaemic control, and emphasizes the importance of individualised targets, balancing the benefits of achieving targets without incurring undue risk of hypoglycaemia or other adverse effects, and considering the risk profile of the patient.

- In Chapter 7 on prevention of cardiovascular disease in diabetes mellitus, recommendations on decision-making in the area of therapeutics have been updated and harmonised with current local guidance on lipid, blood pressure and cardiovascular management. Target blood pressure ranges and LDL levels are discussed, as well as the role of antiplatelet therapy.

- 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 to include developments such as intravitreal injection of anti-vascular endothelial growth factor in patients with diabetic macular oedema.

- Chapter 11 on pre-gestational and gestational diabetes has been updated. Women at high risk for gestational diabetes, but who are not found to have glucose intolerance in early pregnancy, are now recommended to be re-evaluated with a 75 gram OGTT at 24-28 weeks gestation.

- Chapter 13 is a new chapter outlining key principles in the management of the adult with type 1 diabetes, relevant to the primary care healthcare professional.

1.5 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 supersede 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.

Future revisions may include management of hypoglycaemia in persons with diabetes, and evolving areas like bariatric surgery and pancreas/islet cell transplantation.

2 Classification of diabetes mellitus

2.1 Definition of diabetes

Diabetes mellitus is a heterogenous metabolic disorder characterised by presence of hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. 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.

2.2 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 recognised 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[1] and the WHO Consultation in 1998,[2] 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 attributable to an autoimmune process, i.e. *immune-mediated*.

Markers for type 1 immune-mediated diabetes include autoantibodies to islet cell (ICA), insulin (IAA), glutamic acid decarboxylase (GADAb), and tyrosine phosphatases IA-2 and IA-2β. Only testing for ICA and GADAb are available locally.

In Singapore, GADAb and ICA were detectable in up to 40% and 20% of type 1 diabetes, respectively. No autoimmune markers were found in more than half of subjects with type 1 diabetes.[3]

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 diabetes though lacking in obesity, and with difficulty in achieving glycaemic control using oral hypoglycaemic agents, progressing quickly to an insulin-requiring state (Latent Autoimmune Diabetes of Adulthood – LADA).

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

Characterised 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. [4-5]

The risk of developing type 2 diabetes is associated with increasing age, obesity and lack of physical activity. The risk is already significantly higher even in Singaporean Chinese with normal body mass index (BMI), rising further with increasing BMI.[6] Women with prior gestational diabetes and individuals with hypertension and dyslipidaemia are at risk as well.

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.

Ketosis prone diabetes

It is increasingly clear that a category of persons with clinical phenotype of type 2 diabetes are more susceptible to develop ketoacidosis without any precipitating cause. These subjects are usually young, generally obese with a strong family history of diabetes and a low prevalence of autoimmune markers. Impairment of insulin action and secretion may be demonstrable at presentation, but β-cell function improves significantly with aggressive glycemic control such that insulin therapy may be discontinued in these individuals within several months, usually followed by a period of near-normoglycemia that may last for months or years. This variant has also been termed previously as idiopathic type 1 diabetes, atypical diabetes or Flatbush diabetes. Its exact place within the conventional classification of diabetes is still unclear. A proposed Aβ classification system divides this group into those with autoimmune disease with preserved (A+β+) or absent (A+β-) β-cell function, and those without autoimmunity with preserved (A-β+) or absent (A-β-) β-cell function. Subjects with poor β-cell function tend

to require exogenous insulin, while A-β+ subjects tend to be able to achieve adequate glycemic control without exogenous insulin.[7]

Gestational diabetes (GDM)

The definition for GDM was revised in 2008 by the International Association of Diabetes and Pregnancy Study Groups (IADPSG). GDM is defined as the onset or first recognition of any degree of glucose intolerance during pregnancy.[8] This category does not include women with glucose intolerance that predates the pregnancy, whether already known to have diabetes or previously unrecognised and discovered only during the first antenatal visit. The definition applies irrespective of whether insulin is used for treatment, or whether the condition persists after pregnancy.

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. These include genetic defects of β-cell function or insulin action, diseases of the exocrine pancreas (pancretitis, pancreatectomy) as well as diabetes induced by other endocrinopathies (Cushing's syndrome, acromegaly, glucagonoma, phaeochromocytoma, hyperthyroidism), drugs (nicotinic acid, glucocorticoids, thiazides, interferon, diazoxide), toxins and infections (congenital rubella, cytomegalovirus).

Monogenetic defects of β-cell function, of which several subtypes exist, are characterised by early age of onset of hyperglycaemia, strong family history of diabetes displaying autosomal dominant pattern of inheritance, absence of autoimmunity and usually low insulin requirement with relative ease in achieving glycaemic control with sulphonylureas (Maturity Onset Diabetes of the Young – MODY). Genetic testing is available locally only in certain research laboratories.

2.3 Summary

Diabetes mellitus is classified according to aetiological types:

a) Type 1 diabetes mellitus (immune-mediated β-cell destruction, usually leading to absolute insulin deficiency).

b) Type 2 diabetes mellitus (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect, together with insulin resistance), including a variant who are susceptible to ketoacidosis.

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

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

3 Diagnosis and screening of diabetes mellitus in Singapore

3.1 Introduction

In the 2010 National Health Survey,[9] diabetes mellitus was found to affect 11.3% of our population, up from 8.2% in 2004. It is associated with considerable mortality and morbidity from chronic complications. In Singapore, it is associated with a 3-fold increase in mortality[10] (most of which is related to cardiovascular disease) and a three to seven-fold increase in the risk of coronary artery disease.[11]

Early and aggressive treatment of diabetes mellitus 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)[12-19] and microvascular disease (retinopathy, nephropathy, neuropathy).[15,20-28] Intensive lifestyle modifications, treatment of hyperlipidaemia with statins, counselling for smoking cessation, control of blood pressure with a Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) or a Angiotensin Receptor Blocker (ARB) has been found to be cost-effective in the prevention of potential complications of diabetes mellitus.[29]

It is therefore important to detect individuals with diabetes mellitus so that appropriate therapeutic measures can be taken to minimise the morbidity caused by this devastating disease. At the same time, when a diagnosis of diabetes mellitus is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and life-long.

3.2 Objective

It is the objective of the workgroup to provide recommendations regarding the screening and diagnosis of diabetes mellitus that are appropriate for our population. To achieve this, the workgroup closely examined the recommendations of the American Diabetes Association[30] (ADA) and the World Health Organization/International Diabetes Federation[31] (WHO/IDF). In addition, we took into account data derived from our own population.

3.3 Diagnosis of diabetes mellitus

D In patients with hyperglycaemic crisis, diabetes mellitus can be diagnosed without further testing. [30]

Grade D, Level 4

B In patients with typical symptoms, diabetes mellitus can be diagnosed if any one of the following is present. [32-34]

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

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

Grade B, Level 2++

D When two different tests are available for the same patient and the results for both tests are above the diagnostic thresholds, the diagnosis of diabetes is confirmed. [35]

Grade D, Level 4

D When two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point (usually the fasting plasma glucose or 2-hour post-challenge glucose) should be repeated. [30]

Grade D, Level 4

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.

Oral glucose tolerance test (75 g glucose) is performed in accordance to WHO recommendations. The 1-hour post-challenge glucose is not useful for the diagnosis of diabetes mellitus.

Because of its greater simplicity and greater reproducibility when compared to the 2-hour post-challenge glucose, the fasting plasma glucose (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 2-hour post-challenge

glucose ≥11.1 mmol/l as non-diabetic.[36] Therefore, in line with the recommendations of the World Health Organization,[31] we recommend that all subjects FPG from 6.1 to 6.9 mmol/l be subjected to an oral glucose tolerance test (OGTT) to determine the glycaemic status precisely.

D Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus.[1]

Grade D, Level 4

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.[31, 36]

Grade B, Level 2++

D If a second test fails to confirm the diagnosis, barring a laboratory error, such patients are likely to have test results near the margins of the threshold for a diagnosis. The healthcare professional might opt to follow the patient closely and repeat the testing in 6-12 months.[30]

Grade D, Level 4

GPP HbA_{1c} is not recommended as a screening and diagnostic tool for diabetes mellitus until its performance in our multi-ethnic population has been evaluated.

GPP

In coming to this conclusion, the committee considered the incomplete correlation between HbA_{1c} and average glucose in certain individuals, including those of different ethnic groups.[37-42] In addition, the HbA_{1c} can be misleading in patients with certain forms of anaemia and haemoglobinopathies, which may also have unique ethnic or geographic distributions. The impact of these factors has not yet been established in our population. Furthermore, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, HbA_{1c} may not be significantly elevated despite frank diabetes.

Figures 1 and 2 are flow charts which show a recommended diagnostic strategy.

Figure 1 Flowchart for the diagnosis of diabetes mellitus

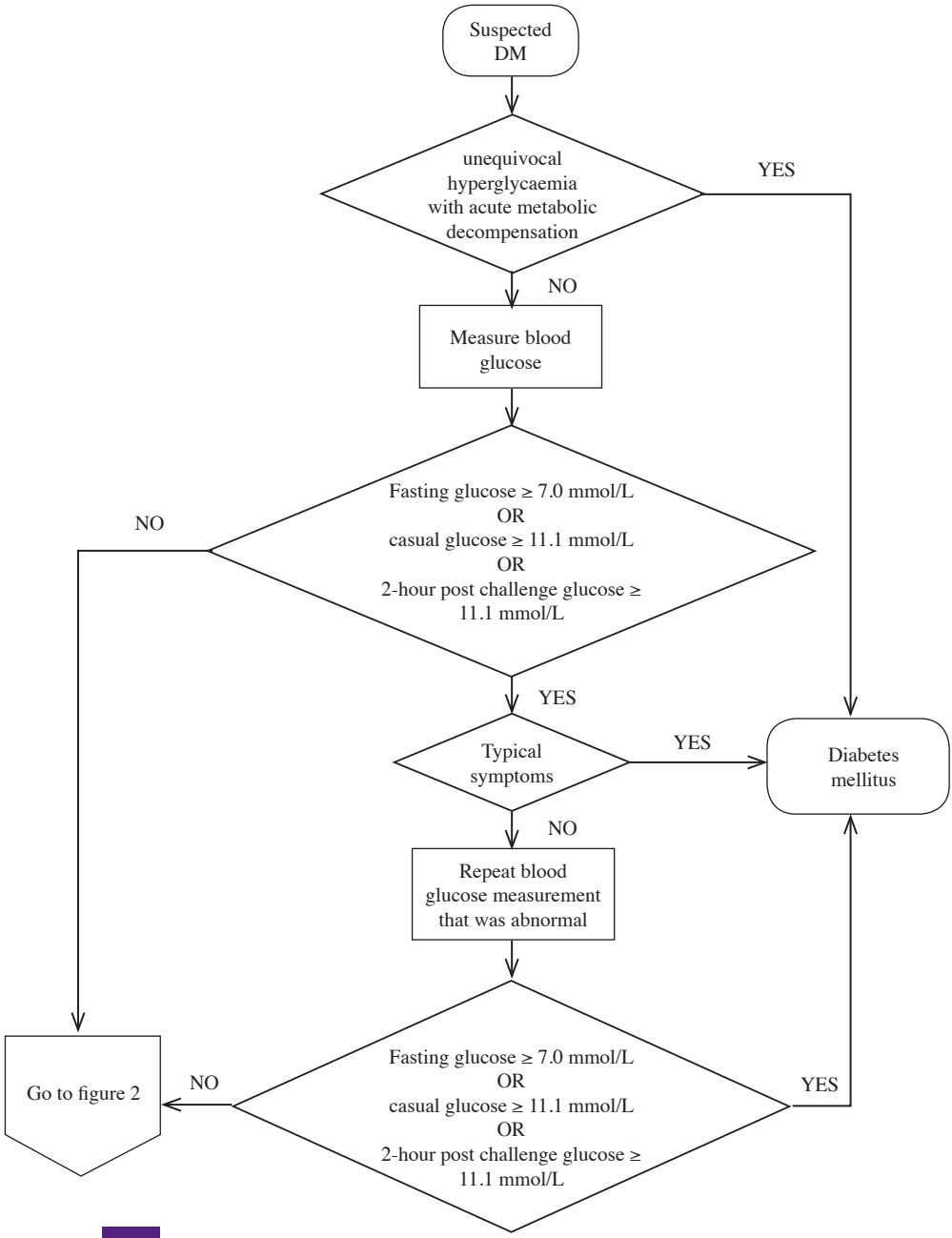
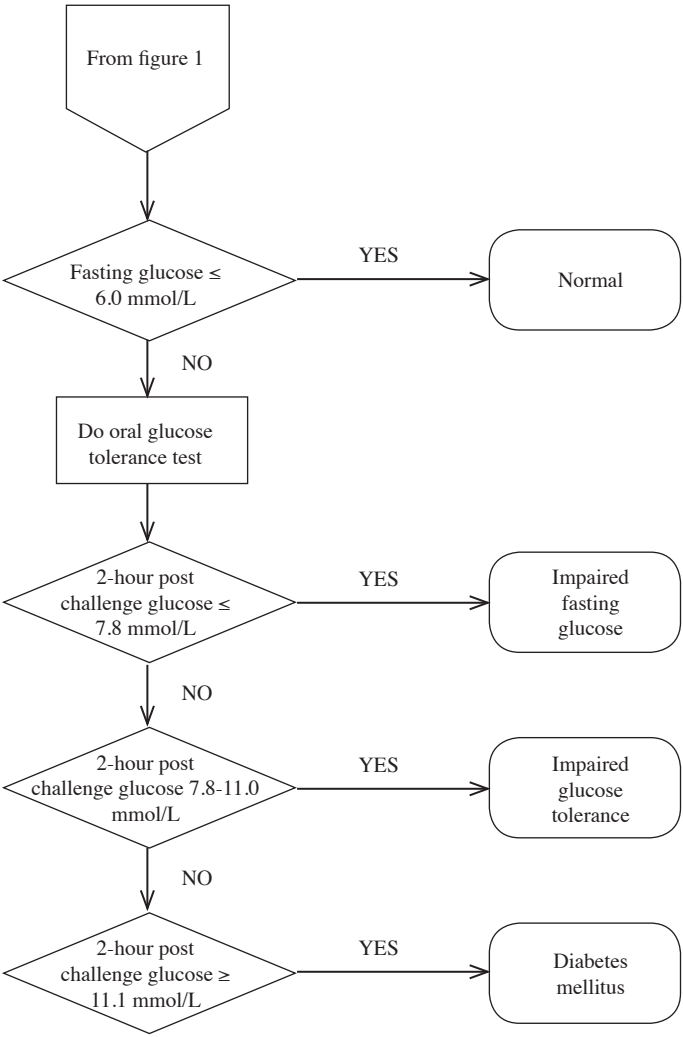


Figure 2 Flowchart for the diagnosis of diabetes mellitus when fasting glucose is not ≥ 7.0 mmol/L or casual / 2-hour post-challenge glucose is not ≥ 11.1 mmol/L



3.4 Other categories of glucose tolerance

Both the ADA and the WHO recognise states of glucose metabolism intermediate between normal glucose tolerance and DM. In addition to impaired glucose tolerance (IGT), an intermediate category based on the fasting plasma glucose (FPG), termed impaired fasting glucose (IFG), has been recognised by the ADA1 and the WHO.[31] These two intermediate categories represent an increased risk for the development of DM and cardiovascular disease.

B Intermediate states of glucose metabolism termed impaired fasting glucose and impaired glucose tolerance should be recognised as defined in Table 1.[31, 43]

Grade B, Level 2++

Table 1 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

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.[44] This was predicated on the belief that this lower level better predicts future diabetes mellitus and cardiovascular disease. The WHO has recommended retaining the existing definition of IFG.[31] The committee has examined the data and arguments for and against this adoption of a new cut-off point for the diagnosis of impaired fasting glucose including data in the Singapore population.[43] We believe that the benefits of the adoption of this new cut-off point are uncertain at this time. As such, we have retained the definition of IFG as FPG from 6.1- 6.9 mmol/l.

3.5 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 on Screening for Cardiovascular Disease and Risk Factors (1/2011).[45] Screening for diabetes mellitus is cost-effective for the population at large from the age of 40 years and is more cost-effective in the groups with hypertension and obesity.[46] In a modelling done by Kahn et al, screening for type 2 diabetes mellitus was shown to be cost-effective when initiated between the ages of 30 and 45 years old in the American population with repeated screening every 3 to 5 years.[47] Screening for both pre-diabetes and diabetes with lifestyle and pharmacological interventions has also been shown to be cost-effective in the UK population.[48]

D Screening should be considered in adults of any age who have one or more risk factors for diabetes. In those without risk factors, testing should begin at 40 years.[46-47]

Grade D, Level 4

D 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).[30]

Grade D, Level 4

Risk factors for diabetes include:

- Overweight/obesity (body mass index ≥25.0 kg/m^2)
- First degree relative with diabetes mellitus
- High risk race/ethnicity
- Women who have delivered a baby 4 kg or more; or previously diagnosed with gestational diabetes mellitus
- Hypertension ≥140/90 mmHg) or on therapy for hypertension
- HDL cholesterol level <1.0 mmol/l (male), <1.3 mmol/l (female) and/or triglyceride level ≥2.2 mmol/l
- Women with polycystic ovarian syndrome
- IGT, or IFG on previous testing
- History of cardiovascular disease

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

a) We wish to emphasise that the aforementioned recommendations are based on plasma glucose measured in an accredited laboratory.

b) Plasma (collected with anticoagulants) glucose and serum (collected without anticoagulants) glucose can differ by as much as 5%.[36] 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.

c) Plasma glucose will decline if the blood sample is not processed within 60 minutes of blood collection.[37] A tube containing a glycolysis inhibitor such as sodium fluoride should be used for collecting the sample if the blood cannot be processed within 60 minutes.

d) Glucometers are suitable for the evaluation of glycaemic control to evaluate adequacy of therapy. Glucometers should not be used for the diagnosis of diabetes mellitus. 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.

4 Lifestyle modification

4.1 Introduction

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

- Medical nutrition therapy
- Physical activity and exercise
- Avoidance of smoking

4.2 Medical nutrition therapy

Medical nutrition therapy in diabetes addresses not only glycaemic control but other aspects of metabolic status as well, including dyslipidaemia and hypertension - major risk factors for cardiovascular disease.[49]

D Individuals who have diabetes should receive individualised medical nutritional therapy as needed to achieve treatment goals, preferably provided by a dietitian familiar with the components of diabetes medical nutrition therapy.[50]

Grade D, Level 4

Effectiveness of medical nutrition therapy has been documented to decrease HbA_{1c} levels by approximately 1–2%, in type 1 and type 2 diabetes.[51] In type 2 diabetes, nutritional intervention has the potential to further improve glycaemic control in patients with unsatisfactory HbA_{1c} despite optimised drug treatment.[52]

Dietary management must be appropriate to the patient's dietary habits, cultural, ethnic practices and activity status.

GPP Special attention should be paid to the diabetic patient's dietary requirements during periods of sickness, fasting, travel and exercise.[53]

GPP

D A diet for diabetes should contain a good balance of carbohydrate, protein and fat, adjusted to meet the individual's metabolic goals and preferences.[50]

Grade D, Level 4

D Individualised meal planning for diabetes should include optimisation of food choices to meet recommended dietary allowance for all micronutrients,[50] providing adequate vitamins and minerals.[54]

Grade D, Level 4

Carbohydrate intake and available insulin are the primary determinants of postprandial blood glucose levels.[55] Therefore, managing carbohydrate intake is a primary strategy for achieving good glycaemic control in both type 1 and type 2 diabetes.[55] Monitoring carbohydrate intake, whether by carbohydrate counting, appropriate food choices or by experience based estimation, remains a key strategy in achieving glycaemic control.[50, 56]

There is little evidence for the ideal carbohydrate composition in the management of hyperglycaemia in diabetes.

B Meal and snack carbohydrate intake for diabetes should be consistently distributed throughout the day, on a day-to-day basis, as consistency in carbohydrate intake has been shown to result in improved glycaemic control. [55]

Grade B, Level 2+

D Consumption of macronutrients is based on recommended dietary allowance (RDA) for healthy eating; 50-60% of total energy from carbohydrates should be encouraged.[54, 57-59]

Grade D, Level 4

Diets too low in carbohydrates may eliminate too many foods that are important sources of vitamins, minerals, fibre and energy.[55]

In persons with type 1 diabetes, priority should be to integrate insulin into the individual's dietary and physical activity pattern. For individuals receiving basal-bolus therapy, matching insulin to the amount of carbohydrate consumed, on a meal by meal basis (carbohydrate counting and insulin dose adjustment) is an effective

strategy in improving glycaemic control, quality of life and general wellbeing. [60-62]

In overweight and obese insulin resistant individuals with type 2 diabetes, a modest weight loss of 5% of body weight is associated with decreased insulin resistance, improved measures of glycaemia, lipaemia and blood pressure.[63] Emphasis should be placed on lowering caloric intake and promoting weight loss for the overweight patients. There is clear evidence that a weight loss of 5-10% of initial body weight through intensive lifestyle intervention (dietary modification and physical activity) is associated with significant improvements in cardiovascular risk factors and HbA_{1c} at one year in overweight and obese patients with type 2 diabetes.[64-65] These benefits were observed to be sustainable over a four year period . [66]

B If weight reduction is needed, it should be attempted gradually (0.25 to 1.0 kg/week). In overweight or obese patients with type 2 diabetes, a weight loss of 5-10% of body weight achieved through lifestyle interventions is a realistic goal.[55]

Grade B, Level 2+

The use of glycaemic index and load may provide a modest additional benefit over that observed when total carbohydrate is considered alone.[50, 52] There are however conflicting evidence with regards to the benefits of the use of glycaemic index (GI) in the management of diabetes.[67-68] Variability of GI responses from carbohydrate-containing foods within and among individuals exist.[69]

For individuals with diabetes and normal renal function, dietary intake of protein is similar to that of the general public and usually does not exceed 20% of energy intake.

D Dietary protein intake of approximately 15-20% of daily energy intake is appropriate for most patients with type 2 diabetes.[56]

Grade D, Level 4

D It is recommended that total calories from fat intake be kept to <30% of total calorie intake in diabetic patients.[57]

Grade D, Level 4

There is strong evidence that reductions in saturated fat and replacement with unsaturated fats are effective in reducing the risk of cardiovascular disease.[52] The aim is to limit saturated fat intake to <7% of total calories.[49]

D Trans fats should be limited to 1% of total energy intake[57] and cholesterol intake (<200mg daily) to reduce risk for cardiovascular disease.[56,58-59] These goals are similar for individuals with pre-existing cardiovascular disease.[53]

Grade D, Level 4

Consumption of fish rich in n-3 unsaturated fats is encouraged at least twice a week.

B Recommendations for fibre intake for people with diabetes are similar to the recommendation for the general population. A daily consumption of a diet containing 20-35 g of dietary fibre from a wide variety of food sources is recommended.[55]

Grade B, Level 2+

D Sodium intake should be restricted to <2 g per day for diabetic individuals with hypertension.[57]

Grade D, Level 4

D Diabetes patients with poor glycaemic control or who are overweight should abstain from alcohol.[54] If individuals choose to drink, intake should be limited to a moderate amount, as per the general population (no more than two drinks for women per day and no more than three drinks per day for men). [57]

Grade D, Level 4

The use of non-nutritive sweeteners (alternative sweeteners) such as aspartame, saccharin, acesulfame K, neotame and sucralose are generally considered as safe for consumption if levels do not exceed Acceptable Daily Intake (ADI).

B Individuals who choose to use non-nutritive sweeteners should be advised that some of these products might contain energy and carbohydrate from sources that might need to be accounted for.[55]

Grade B, Level 2

4.3 Physical activity and exercise

The overall beneficial effects of exercise in type 2 diabetes are well documented. Exercise in type 2 diabetes leads to improvement in glycaemic control, contributes to weight loss and has a favourable effect on cardiovascular risk factors.[70]

4.3.1 Pre-exercise evaluation

An exercise programme should be tailored for each individual patient to suit his age, aptitude, fitness and interest. Before embarking on a programme more vigorous than brisk walking, a pre-exercise evaluation is important especially in sedentary and older diabetic individuals to identify any cardiovascular disease, hypertension, neuropathy or microvascular retinopathy changes that might contraindicate certain types of exercise and predispose to injury.[71]

There is no definitive evidence to suggest that pre-exercise ECG stress testing for asymptomatic individuals at low risk of cardiovascular disease is beneficial but it may be indicated for higher risk individuals.[72]

D For exercise more vigorous than brisk walking, a pre-exercise physician evaluation is recommended for individuals with diabetes to identify cardiovascular risks and any complications of severe neuropathy or severe diabetic retinopathy that may contraindicate certain activities and predispose to injury.

Grade D, Level 4

4.3.2 Exercise with long term diabetes complications

Exercise may help prevent the onset of early peripheral neuropathy.[73] Studies have shown that moderate walking in individuals with peripheral neuropathy does not increase the risk of foot ulcerations or re-ulcerations.[74-75] Nonetheless individuals should use appropriate footwear and be educated to examine their feet on a daily basis to prevent and detect sores or ulcers.

Exercise and physical activity generally do not adversely affect vision or the progression of non-proliferative diabetic retinopathy or macular

disease. However, in severe background or proliferative retinopathy, activities that dramatically elevate blood pressure such as weight-lifting, heavy Valsalva manoeuvres, and heavy competitive sports may be contraindicated as these may trigger vitreous haemorrhage and retinal detachment.[76]

D Individuals with severe proliferative diabetic retinopathy should avoid activities that greatly increase intraocular pressure and risk of haemorrhage.

Grade D, Level 3

B Individuals with peripheral neuropathy and without acute ulceration may participate in moderate weight-bearing exercise. Comprehensive foot care, use of appropriate footwear and daily foot check is recommended.

Grade B, Level 2+

4.3.3 Recommended physical activity for individuals with type 2 diabetes

Clinical trials that evaluate exercise interventions in type 2 diabetes have used a frequency of three times a week[77] but most current guidelines advocate five sessions a week of moderate activity.[78] Any form of physical activity that uses large muscle groups and causes sustained increases in heart rate has been found to be beneficial.[79] For most individuals with type 2 diabetes, brisk walking is a moderate intensity exercise. There has been more recent evidence to suggest the benefits of resistance training in addition to aerobic exercises to increase optimization of insulin action, muscle mass and endurance.[80-81]

B Individuals with type 2 diabetes should undertake at least 150 mins/week of moderate to vigorous aerobic exercise spread out during at least 3 days of the week, with no more than 2 consecutive days between bouts of exercise.

Grade B, Level 1+

4.3.4 Medication effects on exercise responses

In patients on insulin treatment or secretagogues, physical activity can cause hypoglycaemia if medication dose or carbohydrate consumption is not altered. Hypoglycaemia would be rare in individuals not treated with insulin or insulin secretagogues. Certain precautions can avoid hypoglycaemia.[82-83] These include monitoring of blood glucose levels before and after exercise, adjustment of insulin and secretagogues prior to exercise or consumption of extra carbohydrate prior or during to exercise if exercise is unplanned and glucose level is low.

D Individuals with diabetes, especially those on insulin treatment or secretagogues, may require medication dose adjustments and should receive specific education on the prevention of exercise induced hypoglycaemia.

Grade D, Level 4

4.3.5 Exercise in presence of non-optimal glycaemic control

Hyperglycemia can be worsened by exercise in type 1 diabetes patients who are deprived of insulin for 12-48 hours and ketotic.[84] However individuals with type 2 diabetes generally do not need to postpone exercise because of high glucose levels if they are well, have no ketosis and are adequately hydrated.[72]

4.4 Avoidance of smoking

Studies show enhanced macrovascular and microvascular disease as well as increased mortality in individuals with diabetes who smoke.[85] Assessment of smoking status as well as smoking cessation counseling and support should be a routine component of diabetes care.

C Individuals with diabetes should be encouraged to stop smoking.

Grade C, Level 3

4.5 Diabetes Self-Management Education (DSME)

Diabetes Self-management Education (DSME) is an integral component of effective diabetes management and is necessary to improve patient outcomes. It is an ongoing process of facilitating the knowledge, skill and ability needed for diabetes self-care. This should start at the time of diagnosis, and continue throughout the person's lifetime.

DSME has shown benefits in clinical outcomes through HbA_{1c} lowering, improving systolic blood pressure control, weight management and increasing success of smoking cessation. Positive psychosocial outcomes are shown with regards to quality of life and levels of depression.

Current practices of self-management involve a skills-based approach that help people with diabetes make informed decisions, cope with demands of daily living and make changes in behaviour to improve outcomes. This is consistent with shifting the focus to a patient-centric model, working in collaboration with healthcare providers, family, and the community.

A sample program for basic diabetes education might include:

- How diabetes affects the body and the interrelationship of medication, nutrition, physical activity and stress
- Self-monitoring of blood glucose and explanation of home blood glucose goals
- Recognition, treatment and prevention of hyperglycaemia and hypoglycaemia
- Sick day management
- How to access effective care, information updates and patient education
- To keep patients informed of the routine diabetes complications' screening that are required

The American Association of Diabetes Educators (AADE) has identified 7 key behaviours, known as the **AADE7 Self-Care Behaviors™** framework, that lead to better patient self-management of diabetes.

1. **Healthy eating**—The effect of food on blood sugar, sources of fat and carbohydrates, effective meal planning, and resources that patients can use to make wise food choices.
2. **Being active**—Developing an activity plan for patients and talking about ways to overcome common barriers to increased physical activity.
3. **Monitoring**—Information on blood sugar, blood pressure, and other diabetes monitoring equipment. Educators can teach proper use of the equipment, how often and when to test, appropriate target ranges, and how to interpret test results.
4. **Taking medication**—How the medicines work, potential side effects, timing and frequency of administration, and what happens if patients don't take their medication as prescribed.
5. **Problem solving**—Helping patients develop effective coping strategies for the variety of health-related situations that may arise due to diabetes.
6. **Reducing risks**—Teaching the importance of self-care behaviours, such as quitting smoking, having regular eye and foot examinations, monitoring blood pressure and blood sugar, and keeping personal healthcare records.
7. **Healthy coping**—Working with patients to identify psychological and social factors that affect their health and helping them continue with effective self-care behaviours.

B People with diabetes should receive Diabetes Self-Management Education (DSME) when their diabetes is diagnosed and as needed thereafter.[86-87]

Grade B, Level 2+

4.6 Psychosocial care

Psychological and social factors can significantly impact on a person's ability to cope and self-manage, especially with a chronic disease like diabetes. It is important to identify any potential barriers in dealing with diabetes as early as possible. One of the key opportunities for screening of psychosocial status occurs at the point of diagnosis or first presentation. Other opportunities include during regularly scheduled management visits and hospitalisations. It is however also important to re-assess the psychosocial status at discovery of complications, when glucose control seemed erratic or problematic and when there are indications that adherence to the diabetes regimen has been difficult.

Issues known to impact self-management and health outcomes include but are not limited to:

- Attitudes towards the illness,
- Grief over loss of healthy status, or over diabetes complications,
- Individual's help seeking behaviours,
- Level of motivation and readiness to change,
- Expectations regarding medical management and outcomes, affect / mood,
- General and diabetes-related quality of life,
- Diabetes-related distress,
- Availability and accessibility of resources (financial, social, and emotional), and
- Psychiatric history

4.7 Diabetes and depression

The stress of coping with a chronic and demanding condition like diabetes has been linked to higher incidence of depression in diabetes. It is associated with reduced quality of life and higher distress level in particular diabetes related distress, as self-care behaviour is compromised in patients with higher depressive symptoms. Depression is also known to impact on glucose levels and unstable glucose level can also worsen depression.

Symptoms to watch out for may include:
Extended period of moodiness with any or all of the following:

- Feelings of despair
- Inappropriate sense of guilt
- Sleep disturbance
- Weight loss
- Appetite changes
- Loss of interest in daily activities
- Suicidal thoughts

Indications for referral to a mental health specialist for professional help may include:

- Depression with the possibility of self-harm
- Debilitating anxiety (alone or with depression)
- Indications of an eating disorder or
- Cognitive functioning that significantly impairs judgment

Other psychological issues to be aware of are obsession, fear and anxiety, frustration, guilt, embarrassment, non-adherence, pessimism and learned helplessness.

Although the clinician may not feel qualified to treat psychological problems, utilizing the patient-provider relationship as a foundation for further treatment can increase the likelihood that the patient will accept referral for other services. It is important to establish that emotional well-being is part of diabetes management.

D Assessment of psychological and social wellbeing should be included as an ongoing part of diabetes management.[86-87]

Grade D, Level 4

4.8 Helping patients cope

D Clinicians should provide the following psychosocial support to patients during the diagnosis phase of diabetes management:

- Provide medical information and psychological support
- Be accessible and sensitive to patient's needs
- Provide information and repeat if necessary as they may not retain much at this stage
- Introduce to other patients to get them support and an accepting environment
- Involve other family members if necessary[86-87]

Grade D, Level 4

D Clinicians should provide the following psychosocial support to patients during the maintenance phase of diabetes management:

- Motivate patient and family to maintain optimal control
- Create an individualised workable regimen and help patient adhere to it
- Ensure good support from diabetes team
- Check for signs of diabetes burnout
- Consider educational intervention
- Follow up and review behavioural changes
- Modify treatment if necessary[86-87]

Grade D, Level 4

D Clinicians should provide the following psychosocial support to patients during the complications phase of diabetes management:

- Giving them the space to vent and providing them with a lot of realistic reassurance is important.
- Do not overwhelm with information but allow for grieving first.
- Gentle motivation to encourage patients to maintain maintain adherence to treatment regimen and possibly revising some of the information or education will be helpful.
- Counselling is important but needs to be timely.[86-87]

Grade D, Level 4

Short term complications like recurrent diabetic ketoacidosis or severe hypoglycaemia can create a sense of vulnerability, loss of control and anxiety in patients. Reassuring patients and problem solving can help alleviate these emotions.

Long term complications (like blindness, amputation, sexual dysfunction, renal failure) can cause strong sense of anger and resentment in patients.

4.10 Role of community and peer support

D Patients with diabetes should be encouraged to find support from other persons and families living with diabetes and community programmes which reinforces diabetes education and promotes living well with diabetes. These community based programmes provide a safe and accepting environment for learning and sharing with others who live with the same condition. [86-87]

Grade D, Level 4

Being part of a support network helps to alleviate loneliness, alienation and many of the frustrations of coping with a chronic condition like diabetes.

5 Pharmacotherapy

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 (hyperglycaemic and hypoglycaemic emergencies) and chronic complications.

All patients with type 1 diabetes need insulin treatment. Type 2 diabetes is generally treated with oral agents when diet and exercise fail to control glycaemia.[88] Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of illness.[89] Multiple pharmacological agents may be needed to maintain target glucose control. Two or more oral agents, or insulin therapy either alone or in combination with oral agents, may be required.[90] Therefore, it is important to remember that frequent refinement of the therapeutic regimen 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.

The optimal management 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)[91] and pancreatic β-cells[92] 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.[93] 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.[94] Hence, when a subject presents

with diabetes, multiple defects in metabolism have already been established.

5.2 Oral glucose lowering agents

Currently approved oral agents for the treatment of type 2 diabetes in Singapore include insulin secretagogues (sulphonylureas, meglitinides), biguanides, alpha-glucosidase inhibitors, DPP-4 (dipeptidyl peptidase-4) inhibitors and thiazolidinediones. Insulin secretagogues, which include sulphonylureas[95] (tolbutamide, glibenclamide, glipizide, gliclazide, glimepiride) or non-sulphonylureas[96] (nateglinide, repaglinide) stimulate pancreatic insulin release. Biguanides (metformin) decrease hepatic glucose release, enhance peripheral glucose disposal and delay glucose absorption.[97] Alpha-glucosidase inhibitors (acarbose) slow the digestion and absorption of starch and sucrose in the gut, thereby reducing the increase in postprandial blood glucose.[98] DPP-4 inihibitors prevent the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) and enhance glucose-stimulated insulin secretion (incretin action). GLP-1 and GIP act on the pancreatic β-cell to increase insulin release, and GLP-1 also acts on the α-cell to suppress glucagon release and hepatic glucose production. Thiazolidinediones (rosiglitazone and pioglitazone) enhance tissue sensitivity to insulin in muscle and liver through activation of intracellular receptors.[99-100]

Sulphonylureas may increase the risk of hypoglycaemia. Hypoglycaemia is not commonly seen with metformin, alpha-glucosidase inhibitors or DPP-4 inhibitors unless combined with insulin or sulphonylureas.

B Long-acting sulphonylureas e.g., chlorpropamide and glibenclamide, carry a high risk of hypoglycaemia and are not recommended.[101]

Grade B, Level 2^{++}

5.3 Guidelines for oral agent therapy

Therapy for type 2 diabetes encompasses medical nutritional therapy, exercise and lifestyle modification, patient education and empowerment for self-management, and pharmacotherapy.

A Patients with type 2 diabetes may initially be treated with lifestyle modification (diet and exercise)[102] unless they are symptomatic or severely hyperglycaemic (i.e. random blood glucose >15 mmol/l or fasting blood glucose >10 mmol/l) – in which case pharmacological therapy should be initiated together with lifestyle intervention.

Grade A, Level 1+

A Oral glucose lowering agents should be started if glycaemic targets are not achieved in a timely and appropriate manner.[102-103]

Grade A, Level 1+

A If glycaemic targets are not reached with a single oral agent, combination therapy with one or more agents[104] (including insulin) from other classes may be considered. However, one would need to monitor carefully for adverse events such as hypoglycaemia or fluid retention.

Grade A, Level 1+

A Insulin therapy should be considered, 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).[105]

Grade A, Level 1+

The choices of oral drug therapy for type 2 diabetes have become extremely complex with many possible permutations. The physician must use good clinical judgment about the best combinations for the patient with diabetes, and decisions should be tailored to individual needs of the patient.

Metformin is the preferred choice for first-line oral glucose lowering therapy. A recent review covering 70,000 patient-years of exposure to metformin in prospective comparative trials or observation cohort studies, concluded that metformin is not associated with increased risk of lactic acidosis.

Type 2 diabetes is a progressive condition in which β-cell function deteriorates with increasing duration of diabetes. Therapy with multiple pharmacological therapies is often needed to maintain target glucose control.

A Metformin is usually considered first-line pharmacotherapy, and sulphonylureas / dipeptidyl peptidase 4 (DPP-IV) inhibitors / alpha-glucosidase inhibitors are reasonable alternatives as first-line pharmacotherapy.[17, 102, 106]

Grade A, Level 1+

A For type 2 diabetes, two or more oral agents, or insulin therapy, either alone or in combination with oral agents, may be required.[107-109]

Grade A, Level 1+

Alternatives to metformin as initial monotherapy

Other oral agents are acceptable alternatives to metformin as initial monotherapy, if the person does not tolerate metformin, or where metformin is contraindicated.

A For type 2 diabetes, other oral agents are acceptable alternatives to metformin as initial monotherapy, if the person does not tolerate metformin, or where metformin is contraindicated.[110-111]

Grade A, Level 1+

A In the setting of severely uncontrolled type 2 diabetes (for example, HbA_{1c} >10%, random glucose levels consistently above 16.7mmol/L), the presence of ketonuria, or symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy in combination with lifestyle intervention may be the initial treatment of choice.[102-103]

Grade A, Level 1+

The following points should be considered in the choice of the oral agent:[112]

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. In addition, age-related decline in cardiac function and risks of volume overload are issues to consider when using thiazolidinediones. Sulphonylureas (especially long-acting preparations), insulin secretagogues and insulin, can cause hypoglycaemia. In elderly patients, initiating

therapy with low-dose, short-acting oral glucose lowering agents is recommended.

D In elderly patients, initiating therapy with low-dose, short-acting oral glucose lowering agents is recommended.[112]

Grade D, Level 4

2. Weight of patient / Body Mass Index

Metformin remains the oral agent of first choice regardless of body weight.

3. Renal / hepatic 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. Thiazolidinediones may cause fluid retention, particularly in patients with renal dysfunction. Metformin is usually contraindicated in the presence of severe renal or hepatic insufficiency as it may be associated with lactic acidosis. It is advisable to cease metformin usage if the eGFR is below 30ml/min/1.73m^2, and to use with caution in those at risk of a sudden deterioration in renal function and those with eGFR <45 ml/min/1.73m^2.

D Metformin is usually contraindicated in the presence of severe renal or hepatic insufficiency as it may be associated with lactic acidosis.

Grade D, Level 4

D It is advisable to use metformin with caution in those at risk of a sudden deterioration in renal function and those with eGFR <45 ml/min/1.73m^2 [112] and to cease metformin usage if the eGFR is below 30ml/min/1.73m^2.

Grade D, Level 4

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 (in particular, rosiglitazone) are contraindicated in patients with acute coronary syndome, ischaemic heart disease, and all classes of heart failure

(including New York Heart Association (NYHA) Functional Classification Class I/II heart failure patients) and are also not recommended for use in patients with peripheral arterial disease

D Metformin must be used with care in the presence of co-morbid conditions which increase the risk of lactic acidosis (e.g., class III or IV cardiac failure).[112]

Grade D, Level 4

D Thiazolidinediones (in particular, rosiglitazone) are contraindicated in patients with acute coronary syndrome, ischaemic heart disease, and all classes of heart failure (including New York Heart Association (NYHA) Functional Classification Class I/II heart failure patients) and are also not recommended for use in patients with peripheral arterial disease.[112]

Grade D, Level 4

5. Cost-benefit considerations

With the advent of new drug classes and agents in the market, prescribers should remain aware of cost-benefit considerations. Careful deliberation should be given to the agent's short-term and long-term medical benefits/efficacy, impact on patient adherence to medication, profile of adverse effects, and data on clinically relevant clinical end-points.

6. Risk of hypoglycaemia

Some oral glucose lowering medications can cause hypoglycaemia. Hypoglycaemia is more common in older patients, chronic alcohol abuse, and patients with liver or renal disease. Patients on sulphonylureas and meglitinides have the highest incidence of hypoglycaemia because of their pharmacological action of increasing insulin secretion. Of the sulphonylureas, long-acting agents like glibenclamide and chlorpropamide present the highest risk of hypoglycaemia. Combination therapies, especially those regimens containing a sulphonylurea, increase the risk of hypoglycaemia.

7. Patient-centric approach

Treatment choices should be individualised and culturally appropriate, and patients should have the opportunity to make informed decisions on their care and treatment options, in partnership with their healthcare providers.

GPP Treatment choices should be individualised and culturally appropriate, and patients should have the opportunity to make informed decisions on their care and treatment options, in partnership with their healthcare providers.

GPP

The mechanism of action, advantages and disadvantages of major classes of oral glucose lowering agents are shown in Tables 2, 3 & 4 on pages 71-72.

5.4 Optimisation of glycaemic control, after initiation of 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.

5.5 Newer agents

GLP-1 receptor (glucagon-like peptide-1) agonists

Incretin hormones are important mediators of glycaemic homeostasis. GLP-1 (glucagon-like peptide-1) agonists were developed to mimic the effect of endogenous GLP-1 hormone, but with a longer duration of action. Currently available GLP-1 agonists include the GLP-1 mimetic exenatide and the GLP-1 analogue, liraglutide, both of which

are administered via subcutaneous injections. Numerous clinical studies have confirmed the efficacy of GLP-1 agonists for improving glycaemic control with a low risk of hypoglycaemia. The predominant adverse events associated with GLP-1 agonists are gastrointestinal in nature (nausea, vomiting, diarrhea, and the use of exenatide is not recommended in patients with a history of pancreatitis).

D The use of exenatide is not recommended in type 2 diabetes patients with a history of pancreatitis.[113-115]

Grade D, Level 4

5.6 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. In the therapeutic journey, the progressive nature of type 2 diabetes and treatment should be explained and reinforced regularly, and progression to insulin should not be described as failure or punishment. 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.

A All patients with type 1 diabetes 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 1+

D 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, matching of insulin dose and carbohydrate intake, and dose adjustments during sick days, travel, exercise, and changes in food intake.

Grade D, Level 4

Tables 2, 3 and 4 (pg 71-72) list the common types of insulin preparations that are currently available in our local context.

B Insulin therapy should be managed with relevant and regular insulin and hypoglycaemia-related self-management training with the common goal of improved glycaemic control and reduction in risk of severe hypoglycaemia.[60, 116-119]

Grade B, Level 2++

Examples of 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, i.e. neutral protamine Hagedorn (NPH) before breakfast and before dinner, or
  - pre-mixed regular and (NPH) insulins, usually administered 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 once a day, often at bedtime (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.[25] 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.[120-122] The shorter duration of action of these rapid-acting insulin analogues may also lead to a lower incidence of hypoglycaemia.

5.8 Long-acting insulin analogues

Two long-acting insulin analogues, insulin glargine and insulin detemir, are available for use locally.[123-124] These long-acting analogues have virtually no plasma peak, and act for about 18-24 hours,[125] hence allowing once-daily administration as background insulin. Some patients may require twice-daily administration for effective basal therapy. The time of day at which these analogues are injected has no clinically relevant effect on glycaemic control. 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) insulin. Patients on intermediate-acting and long-acting insulin who experience frequent hypoglycaemic episodes related to their peak activity may benefit from the use of these agents which have been shown to achieve better glycaemic control with lower incidence of hypoglycaemia.[126-128] In recent years, observations that glargine has higher affinity for insulin-like growth factor-1 receptor compared to human insulin, theoretically altering mitogenic activity, have raised concerns, but there is currently insufficient evidence to make a recommendation against glargine.

Table 2 - Mechanism of action of available therapeutic options for type 2 diabetes

	Metformin	Insulin secretagogues sulphonylurea	Insulin secretagogues meglitidines / Non sulphonylurea	Thiazolidinedione	Alpha-glucosidase inhibitors (AGI)	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Glucagon-like peptide-1 (GLP-1) agonist
Mechanism of action	Decreased hepatic glucose production	Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Insulin sensitizer	Decreased gut carbohydrate absorption	Inhibits DPP-4 activity, prolongs action of endogenous incretin hormones	Activates (GLP-1) receptors

Table 3 - Benefits of available therapeutic options for type 2 diabetes

	Metformin	Insulin secretagogues sulphonylurea	Insulin secretagogues meglitidines / Non sulphonylurea	Thiazolidinedione	Alpha-glucosidase inhibitors (AGI)	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Glucagon-like peptide-1 (GLP-1) agonist
HbA_{1c} lowering	1-1.5%	1-1.5%	0.5-1.0%	0.5-1.5%	0.5-0.8%	0.5-0.8%	0.5-1.0%
FPG lowering	Moderate	Mild	Mild	Moderate	Neutral	Mild	Mild
PPG lowering	Mild	Moderate	Moderate	Mild	Moderate	Moderate	Moderate
Lower microvascular risk	Proven	Proven	-	-	-	-	-
Others	Well established modality	Well established modality	-	-	-	Low risk for hypoglycaemia	Potential for weight reduction and improved β-cell mass/function

Table 4 – Side effects, cost and management considerations of available therapeutic options for type 2 diabetes

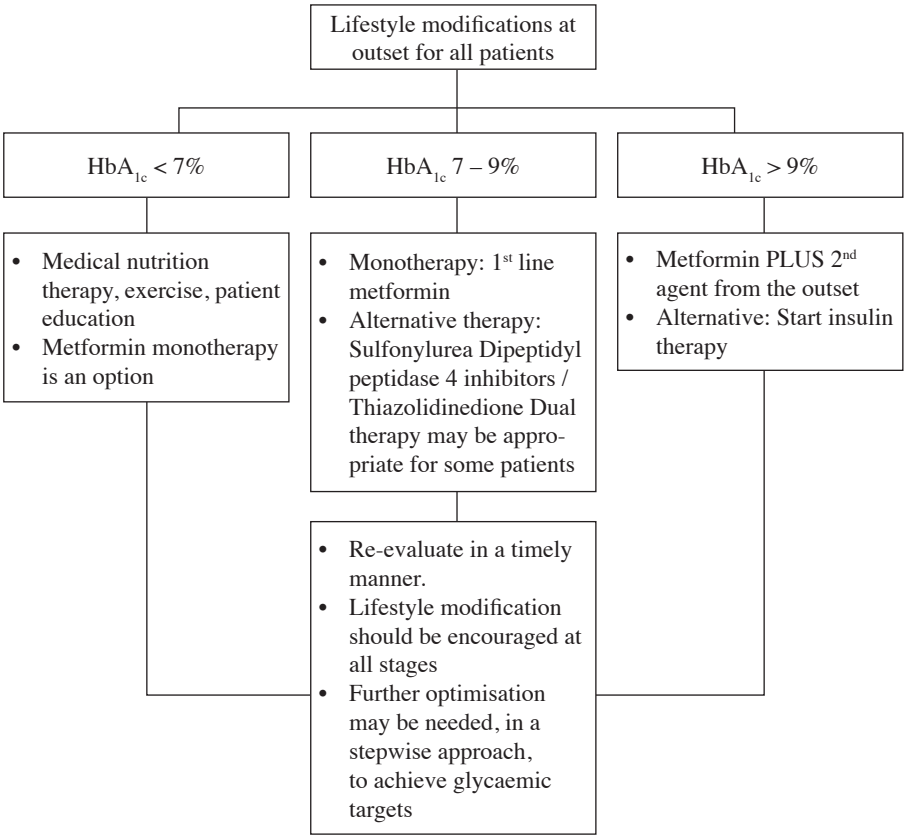
	Metformin	Insulin secretagogues sulphonylurea	Insulin secretagogues meglitidines / Non sulphonylurea	Thiazolidinedione	Alpha-glucosidase inhibitors (AGI)	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Glucagon-like peptide-1 (GLP-1) agonist
Hypoglycaemia	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Neutral
GI symptoms	Moderate	Neutral	Neutral	Neutral	Moderate	Neutral	Moderate
Renal insufficiency	Moderate*	Moderate+	Neutral	Mild	*(Relatively safe)*	Mild**	Mild
Hepatic	Mild	Mild	Mild	Mild	-	Neutral	Contraindicated in past history of pancreatitis
Heart failure	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
Weight gain	*(Mild weight reduction)*	Mild Possibly neutral for slow-release gliclazide[129-130]	Mild	Moderate	Neutral	Neutral	*(Mild weight reduction)*
Fractures	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
Others	-	-	-	-	-	-	Parenteral
Cost	$	$ - $$	$$	$$$	$$	$$$	$$$

* Stop metformin use if the patient has an estimated glomerular filtration rate (eGFR) below 30ml/min/1.73m^2
Use with caution for those at risk of a sudden deterioration in renal function and those with eGFR <45 ml/min/1.73m^2

** Reduce dosage

\+ use lower dose and short-acting sulphonylureas.[131]

Figure 3 Proposed algorithm for initiation of therapy



Foot notes

1) Consider insulin treatment at outset for patients who are markedly symptomatic. The need for long-term insulin should be reevaluated after improvement and stabilization of glycaemic control.
2) Thiazolidinedione: pioglitazone
3) Metformin and renal impairment

eGFR 30ml/min/1.73m^2: usage not recommended

eGFR 31-45 ml/min/1.73m^2 use with caution

5.9 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.[25]

Pre-meal soluble insulin or rapid-acting insulin analogue can be administered by multiple daily injections (MDI) or CSII. Patients with type 1 diabetes are often on a MDI regimen of three to five injections per day of basal/background (intermediate or long acting insulin or insulin analogue) and prandial/mealtime (soluble or rapid acting insulin analogue) insulin. They should also receive instruction on matching of prandial insulin to carbohydrate intake, premeal blood glucose and anticipated activity.

5.10 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.[26]

Introduction of insulin should not be delayed if metabolic control becomes suboptimal.[132] This may be initiated as a bedtime dose of intermediate-acting or long-acting insulin with maintenance of oral agents during the day.

D In type 2 diabetes, introduction of insulin should not be delayed if metabolic control becomes suboptimal.[132] This may be initiated as a bedtime dose of intermediate-acting or long-acting insulin with maintenance of oral agents during the day.

Grade D, Level 4

D When glycaemic control is not achieved despite the addition of basal insulin to oral agents, discontinuing sulphonylureas and switching to premixed twice daily or basal-bolus insulin regimens becomes necessary.[102] However, metformin[133] and α-glucosidase inhibitors[134] 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. Patients with type 2 diabetes who are switched to insulin therapy 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.[135]

Grade D, Level 4

Table 5 Insulin types[136-137]

Insulin Types	Insulin details	Onset	Peak	Duration
Rapid-acting insulins	Human insulin analogues: 1) Insulin lispro (Humalog) 2) Insulin aspart (NovoRapid) 3) Insulin glulisine (Apidra)	 15-30 mins 12-18 mins 12-30 mins	 0.5-2.5 hours 1-3 hours 1.5-3 hours	 2-4 hours 3-5 hours 3-4 hours
Short-acting insulins	Recombinant human regular insulin: 1) (Humulin R) 2) (Actrapid)	 30-60 mins	 2-4 hours	 6-8 hours
Intermediate-acting insulins	NPH (Humulin N or Insulatard)	1-4 hours	8-12 hours	12-20 hours
Long-acting insulins	Insulin glargine (Lantus) Insulin detemir (Levemir)	1-4 hours 1-4 hours	peakless peakless	24 hours 18-24 hours
Premixed Insulins	1) Biphasic (Mixtard 30 or Humulin 30/70): premixed 30% regular insulin + 70% intermediate-acting insulin 2) Biphasic (Mixtard 50 or Humulin 50/50): premixed 50% regular insulin + 50% intermediate-acting insulin 3) Biphasic insulin analogue • (NovoMix 30): premixed 30% insulin aspart + 70% protaminated insulin aspart • (Humalog Mix 25/75): premixed 25% insulin lispro + 75% protaminated insulin lispro	30-60 mins 30-60 mins 10-20 mins 10-20 mins	2-8 hours 2-8 hours 1-3 hours 1-3 hours	24 hours 24 hours 24 hours 24 hours

(Source: Product information from respective package insert)

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.[25-26] Two methods are available to access glycaemic control: patient self-monitoring of blood glucose (SMBG) and glycated haemoglobin (HbA_{1c}).

6.2 Blood glucose monitoring

SMBG by patients should be an integral part of diabetes self-management 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-management.

Indication for SMBG

B Self-monitoring of blood glucose is recommended for patients with type 1 or type 2 diabetes who are using insulin.

Grade B, Level 2^{++}

SMBG is a fundamental component of self-management in patients with insulin-treated diabetes.[138-139] SMBG can guide adjustment of insulin and allows patients to assess whether glycaemic targets are being achieved.[140] Results of SMBG can also be useful in preventing hypoglycaemia in this group of patients.

D Self-monitoring of blood glucose should be considered in the following groups of patients with type 2 diabetes who are not treated with insulin:

- those at increased risk of developing hypoglycaemia or its consequences (e.g., patients who are using sulphonylureas)
- those pregnant patients with pre-existing diabetes or gestational diabetes
- those experiencing acute illness
- those who have failed to achieve glycaemic goals
- those undergoing fasting, for example, during Ramadan

Grade D, Level 4

The evidence for the benefit of routine SMBG in non-insulin treated patients with type 2 diabetes is conflicting. A meta-analysis of SMBG in non-insulin treated patients with type 2 diabetes concluded that some regimen of SMBG was associated with a reduction in HbA_{1c} of 0.4%.[141] However, several recent trials of higher qualities have questioned the clinical and cost-effectiveness of SMBG for non-insulin treated patients with type 2 diabetes. One large randomised controlled trial done in the UK (DIGEM) found no significant effect of SMBG on HbA_{1c} between groups randomised to standard care (no self-monitoring), less intensive SMBG with nurse-practitioner interpretation of results and more intensive SMBG with self interpretation of results. The study also reported a negative impact of SMBG on quality of life and economic analysis indicated it was not cost effective if used routinely.[142-143] A more recent study (ESMON) recruited newly diagnosed patients with type 2 diabetes and a uniform treatment algorithm based on HbA_{1c} targets was applied to both SMBG and non-SMBG groups. At 12 months, HbA_{1c} was reduced in both groups and no significant difference between the groups was observed.[144]

Frequency of self-monitoring of blood glucose

The frequency and timing of SMBG should be determined by the particular needs and goals of the patients. SMBG is particularly important in patients treated with insulin to monitor for and prevent asymptomatic hypoglycaemia and hyperglycaemia.

B Self-monitoring of blood glucose should be carried out 3 or more times daily for patients with type 1 diabetes.

Grade B, Level 2++

For patients with type 1 diabetes, a retrospective cohort study showed that mean HbA_{1c} was significantly decreased in patients who carried out SMBG at least 3 times a day compared to those who performed an average of 1 SMBG a day.[138]

For insulin-treated type 2 diabetic patients, testing 2 or 3 times a day on 2 to 3 days a week would be appropriate. The optimal frequency and timing of SMBG for non-insulin treated patients with type 2 diabetes is unclear, but it should be frequent enough to facilitate reaching glucose targets.

GPP For patients with unstable metabolic control, changes in daily routine, alterations of treatment regimens or acute illness, the frequency of self-monitoring of blood glucose should be increased.

GPP

Methodology and accuracy

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

GPP

Glucometer

With improved technology, most brands of glucometers on 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.

B To ensure optimal benefit from self-monitoring of blood glucose, patients must be educated on the interpretation of glucose levels.[145]

Grade B, Level 1+

GPP 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.

GPP

GPP It is recommended that calibration checks of meters are periodically conducted using standard solutions according to the manufacturer's recommendations.

GPP

Continuous glucose monitoring (CGM)

Although self-monitoring of blood glucose is an integral part of the diabetes self-management in patients with type 1 diabetes, many patients do not routinely monitor glucose levels either post-prandially or overnight, which may leave undetected episodes of hyperglycaemia and hypoglycaemia respectively.[146] Systems that allow continuous monitoring of glucose by means of subcutaneous sensors which measure interstitial glucose levels are now available. These sensors require calibration with SMBG, and the latter are still recommended for making acute treatment decision.

There is currently insufficient data to suggest that CGM should be used routinely in patients with diabetes but CGM may be a useful adjuvant to conventional SMBG in selected adults with type 1 diabetes as an aid to improve glycaemic control. A large randomsied controlled trial of 322 patients with type 1 diabetes showed that adults age 25 years and

older using intensive insulin therapy and CGM experienced significant reduction in HbA_{1c} of 0.5% compared to usual intensive insulin therapy with SMBG.[147]

D Continuous glucose monitoring may be used as a supplemental tool to SMBG in patients with hypoglycaemia unawareness and/or frequent hypoglycaemic episodes.

Grade D, Level 3

6.3 Urine glucose monitoring

B Self-monitoring of urine glucose is not recommended for monitoring of glycaemic status.

Grade B, Level 1+

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.[148] One meta-analysis evaluated the effectiveness of interventions with self-monitoring of urine glucose versus interventions without self-monitoring in terms of HbA_{1c} reduction. The meta-analysis suggests that a very modest improvement in HbA_{1c} of 0.14% is associated with urine testing versus no testing, which is unlikely to be of clinical significance.[149]

6.4 Urine and blood ketone monitoring

A Ketone monitoring should be performed during sustained hyperglycaemia (e.g., blood glucose > 14.0 mmol/l) in patients with type 1 diabetes, especially during acute illness. Blood ketone monitoring is preferable to urine ketone monitoring.

Grade A, Level 1+

Testing for urine and more recently blood ketone is an important part of monitoring in patients with type 1 diabetes. However, there is currently insufficient evidence to recommend routine monitoring of blood ketones for diabetic patients, whether type 1 or type 2. In appropriate circumstances, the detection of ketones in the urine or blood may indicate impending metabolic decompensation and the development of diabetic

ketoacidosis. Such circumstances include sustained hyperglycaemia (e.g., blood glucose >14.0 mmol/l) and acute illness or stress.

Blood ketone monitoring quantifies β-hydroxybutyric acid, the predominant ketone body, and it may be superior to urine ketone monitoring. One small randomised controlled trial compared the benefits of blood ketone monitoring against urine ketone monitoring during sick days in patients with type 1 diabetes.[150] The study showed that the incidence of hospitalisation/emergency assessment was significantly lower in the blood ketone group compared with the urine ketone group although the event rates were small. Blood ketone monitoring was also reported to be preferred by young people with type 1 diabetes.

6.5 Glycated haemoglobin

D Glycated haemoglobin (HbA_{1c}) should be performed routinely in all patients with diabetes, at initial assessment and then as part of follow-up care.[50]

Grade D, Level 4

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. 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. Current HbA_{1c} assays in most parts of the world are aligned to the assay used in the DCCT (Diabetes Control and Complications Trial), so that an individual's risk of complications can be inferred from the result. It is recommended that samples for HbA_{1c} measurements be sent to laboratories with DCCT-aligned assays.

The HbA_{1c} test is subject to certain interferences. Haemoglobin variants and conditions that affect red blood cell turnover (e.g., blood loss, haemolysis) may affect the validity of HbA_{1c} results. These conditions should be considered particularly when the HbA_{1c} results does not

correlate with the patient's clinical condition.[151] Other measures of chronic glycaemic such as fructosamine are available, but their prognostic significance is not as clear as in the case for HbA_{1c}.

D The measurement of HbA_{1c} should be done in laboratories that utilise DCCT-aligned assays (DCCT - Diabetes Control and Complications Trial).

Grade D, Level 4

Frequency of testing

The frequency of HbA_{1c} testing should be determined by the clinical situation, the treatment regimen used, and the judgement of the clinician.

D The following schedule is recommended for HbA_{1c} testing in patients with diabetes:

- 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 D, Level 4

B HbA_{1c} result should be made available at the time that the patient with diabetes is seen.

Grade B, Level 2^{++}

It is reported in a study that availability of HbA_{1c} result during the patient visit increased the frequency of intensification of therapy and lowered HbA_{1c} levels in patients with type 2 diabetes.[152]

6.6 Targets of glycaemic control

D The targets of glycaemic control should be individualised.

Grade D, Level 4

Glycaemic control is fundamental to the management of diabetes as this has been shown to reduce the risk of diabetes-related complications. However, patients striving to achieve the best level of glucose control they can achieve may encounter hypoglycaemia. Therefore glycaemic targets must be individualised to ensure that patients do not incur an undue risk of hypoglycaemia or other adverse effects associated with tight control.[153]

GPP Patients should participate in the process of defining their targets of glycaemic control (See Table 6).

GPP

Table 6 Targets of glycaemic control

Test	Targets
HbA_{1c} * (%)	≤ 7.0% or ≤ 53 mmol/mol
Pre-meal glucose† (mmol/l)	4.0 – 7.0
2-hour post-meal glucose† (mmol/l)	< 10.0

* HbA_{1c} target should be tailored to the individual with diabetes
† Values pertaining to capillary blood sample

The HbA_{1c} target of ≤7.0% or 53 mmol/mol for most non-pregnant adults with type 1 or type 2 diabetes has been shown to reduce the risk of developing microvascular complications and if implemented soon after the diagnosis of diabetes, is associated with lowered risk of macrovascular disease.

A The HbA_{1c} target for most non-pregnant adults with type 1 or type 2 diabetes should be ≤7.0% or ≤53 mmol/mol.

Grade A, Level 1^{++}

The Diabetes Control and Complications Trial (DCCT) is a randomised, controlled trial of intensive versus standard glycaemic control in patients with type 1 diabetes. It provided conclusive evidence that intensive glycaemic control is associated with significantly decreased risk of microvascular complications.[25]

Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycaemic control using regimens that reduce average HbA_{1c} to 7.0% or 53 mmol/mol substantially decreased the risk of microvascular disease in patients with newly diagnosed type 2 diabetes.[26]

Both the DCCT and UKPDS failed to show a significant reduction in cardiovascular disease (CVD) outcomes during the randomised portion of the trials. However, continued follow-up of DCCT subjects in the Epidemiology of Diabetes Interventions and Complications (EDIC) study and the UKPDS cohort showed that early intensive glucose control lowered the risk of macrovascular disease, even though there was a loss of glycaemic separation between the intensive and standard arm subjects during follow-up.[17-18]

B Lowering HbA_{1c} target to ≤6.5% or ≤47.5 mmol/mol may be considered for some patients with type 2 diabetes at doctor and patient judgement, if this can be achieved without significant hypoglycaemia. Such patients include those with short duration of diabetes, long life expectancy and no significant cardiovascular disease.

Grade B, Level 1+

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, intensive glycaemic control in type 2 diabetes was associated with a statistically significant reduction in albuminuria with an HbA_{1c} target of <6.5% or 47.5 mmol/mol compared with standard therapy.[21] Epidemiological analyses of the DCCT and UKPDS also suggest that further lowering of HbA_{1c} from 7 to 6% or 53 mmol/mol to 42.1 mmol/mol is associated with further reduction of microvascular complications, albeit the absolute risk reductions become much smaller.[25-26] As such, selected individual patients, especially those with short duration of disease, long life expectancy and no cardiovascular disease, may adopt lower HbA_{1c} targets than the general goal of <7.0% or 53 mmol/mol if this can be achieved without significant hypoglycaemia.

D Less stringent HbA_{1c} target (e.g., 7.0 to 8.5% or 53 mmol/mol to 69.4 mmol/mol) may be adopted for some patients vulnerable to the harmful effects associated with tight glycaemic control. Such patients include those with very long duration of diabetes, known history of severe hypoglycaemia, advanced atherosclerosis and advanced age.

Grade D, Level 4

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the glycaemic control arm was halted early due to the finding of an increased rate of mortality in the intensive arm compared with the standard arm.[23] The potential cause of this increased mortality has been difficult to pinpoint. This study suggests that the potential risks of very intensive glycaemic control may outweigh its benefits in certain groups of patients, such as those with very long duration of diabetes, known history of severe hypoglycaemia, advanced atherosclerosis and advanced age.

GPP Doctors should be vigilant in preventing hypoglycaemia by reviewing treatment regimens in patients with near-normal HbA_{1c} levels (e.g., <6.0% or 42.1 mmol/mol), especially those treated with insulin or insulin secretagogues.

GPP

7 Prevention of cardiovascular disease in people with diabetes

7.1 Assessment for cardiovascular risk factors in diabetes mellitus

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. The case-fatality is also 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. Prevention of cardiovascular disease is a major goal of therapy in type 2 diabetes mellitus. Apart from hyperglycaemia, persons with type 2 diabetes mellitus often have other co-morbidities including hypertension, dyslipidaemia, and obesity.

7.2 Global cardiovascular assessment

People with diabetes are at higher risk of developing cardiovascular disease than people without diabetes and diabetes has sometimes been regarded as a coronary risk equivalent.[154] There is evidence that amongst people with diabetes, the duration of diabetes[155] and the number of additional cardiovascular risk factors[156] may affect the propensity to develop incident cardiovascular disease. Hence identifying the varying cardiovascular risk factor burden is an integral part of the management of the patient with type 2 diabetes It is clear that the patient with newly diagnosed diabetes, though having a higher risk than somebody of similar circumstances without diabetes, would have lower risk for incident cardiovascular disease than a patient with diabetes with advanced complications as well as other cardiovascular risk factors.

There is epidemiological evidence that amongst people with no known prior coronary artery disease, those with diabetes have higher rates of sudden cardiac death when compared to those without diabetes.[157] In the DIAD (The Detection of Ischemia in Asymptomatic Diabetics) study, approximately 22% of subjects who were asymptomatic of cardiovascular disease, were found to have evidence of myocardial

ischemia using myocardial perfusion imaging at baseline screening.[158] However, at the end of 4.8 years, there was no difference in outcomes between those who were screened when compared to those who were not screened.[159] The authors of the study concluded that there were no grounds to advocate screening using myocardial perfusion imaging even in a relatively high-risk group such as people with diabetes.

Consequently, for asymptomatic patients with type 2 diabetes, instead of imaging studies to identify perfusion defects, a global cardiovascular assessment aimed at identifying cardiovascular risk factors and end organ damage, based on medical history, physical examination, simple laboratory tests is recommended.

7.3 Medical history, physical examination, blood pressure, laboratory tests and ECG

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

History – which should include:

- Smoking
- Hypertension
- Pre-existing cardiovascular disease (including angina, myocardial infarction, stroke, PAD)
- Family history of premature coronary artery disease (non-modifiable)

Physical examination – which should include:

- Assessment for peripheral vascular disease
- Measurement of blood pressure at every visit

Tests – which should include:

- Fasting serum lipids at or soon after diagnosis and at least annually
- Urine microalbumim or protein at least annually
- Serum creatinine and estimation of eGFR (See chapter 8)
- Electrocardiogram (resting) routinely at baseline. Subsequent ECG may be performed when clinically indicated.

GPP

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

The prevention of cardiovascular disease in persons with type 2 diabetes mellitus must take a global approach with intervention targeting all aspects of the disease. Even amongst people with diabetes, the duration of diabetes[2] and the number of additional cardiovascular risk factors, may affect the propensity to develop incident cardiovascular disease.[156] There is compelling evidence that, in general, multiple risk factor management reduces cardiovascular mortality in people with type 2 diabetes.[14]

Although an LDL cholesterol target of 2.6 mmol/L has been recommended for most patients with diabetes, for people with diabetes of short duration (<10 years), without additional cardiovascular risk factors; who for example has LDL cholesterol just above 2.6 mmol/L, it may be acceptable to discuss a period of dietary and lifestyle modification before considering pharmacological therapy. Similarly, the initiation age for antiplatelet therapy for primary prevention of cardiovascular disease, has been pushed back as recent trials in patients with type 2 diabetes, who do not have previous clinical coronary artery disease, have not been able to demonstrate cardiovascular benefits.[160-161]

7.5 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 cardiovascular disease risk associated with type 2 diabetes mellitus. Such therapeutic lifestyle modification should include smoking cessation, medical nutrition, therapy and increased physical activity. Please refer to chapter 4 for a more in depth look at lifestyle modification.

7.6 Management of blood glucose in persons with type 2 diabetes mellitus with a view to minimizing cardiovascular risk

Early epidemiological studies, including an epidemiological analysis of the UKPDS, showed that increasing HbA_{1c} was associated with increasing risk for cardiovascular disease.[162-163] A follow-up study of the UKPDS which originally recruited persons with newly diagnosed type 2 diabetes showed that early intensive blood glucose management (to mean HbA_{1c} of 7.9% in sulphonylurea-insulin group, 8.4% in metformin group) resulted in durable beneficial effects in terms of cardiovascular outcomes on follow-up.[17] However recent trials[21,23,164] in people with long-standing type 2 diabetes (mean duration from 8-12 years) have failed to demonstrate cardiovascular benefits of intensive glucose lowering to mean HbA_{1c} of 6.4% to 6.9%. Taken together, these data imply that intensive blood glucose lowering in people with newly diagnosed diabetes may have potential cardiovascular benefits and these benefits may accrue many years later. However these benefits may not be accrued by intensive glucose lowering to below 6.5% in patients with long-standing type 2 diabetes.

After reports of possible increase in coronary artery events associated with the use of rosiglitazone appeared,[165] the original notion that specific oral glucose lowering agents may have beneficial cardiovascular effects have given way instead to concerns about cardiovascular safety. Although it is felt that the association of use of rosiglitazone with increase in coronary artery disease events has not been conclusively proven,[166] there has been regulatory requirement for pharmaceutical companies manufacturing oral glucose lowering agents to perform trials to study cardiovascular safety and the outcomes of several such trials are awaited.[167] (See chapter on pharmacotherapy).

7.7 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).

7.8 Goals of therapy and levels for the initiation of pharmacologic therapy

B For patients with type 2 diabetes mellitus who have hypertension, an acceptable treatment-initiation and target blood pressure is <140/80 mm Hg.[168,169-170]

Grade B, Level 2+

There is on-going debate on blood pressure targets in patients with diabetes, and differing opinions from various global bodies.[171-172] Currently available best grade evidence suggests that the acceptable target ranges for initiation of therapy as well as treatment goals, are 130-139 mmHg and 70-90 mmHg for systolic and diastolic blood pressure respectively. As with targets for glycemic control and other cardiovascular risk factors like cholesterol levels, it is prudent to always exercise clinical judgement tailored to the individual patient and clinical setting.

The intensive blood pressure arm of the ADVANCE study which evaluated the effects of aggressive blood pressure therapy in patients with type 2 diabetes, achieved a systolic blood pressure of about 135 mmHg and reduced overall mortality as well as cardiovascular mortality over 4.3 years, when compared to control arm although the primary composite macrovascular endpoint was not different.[173] In the ACCORD study the blood pressure attained in the intensive BP arm was 119/64 mmHg and the control arm 133/70 mmHg. The primary composite outcome was no different between the two groups although rates of total as well as fatal stroke were lower in the intensive arm.[174]

However, the intensive arm had significantly more adverse events including hypotension and renal impairment. An epidemiological analysis of the INVEST study also did not show any difference in primary composite endpoint between tight control group (systolic blood pressure <130 mmHg) and usual control group (systolic blood pressure between 130 and 139 mmHg).[175] From these data, it appears that lowering systolic blood pressure below the low 130s may not result in lower total composite cardiovascular endpoints although the ACCORD study suggested some benefit in stroke rate reduction.

A recent meta-analysis which included trials of subjects with type 2 diabetes as well as impaired fasting glucose suggested that most of the benefit in all-cause mortality in the intensive arms was accrued by the trials where the intensive arms had achieved systolic blood pressure of between 130 and 135 mmHg. For the outcomes of cardiovascular mortality, myocardial infarct and heart failure, although there was no statistical difference between the two groups, the point estimate favoured the intensive arm, again mainly driven by the trials where achieved systolic blood pressure was between 130 and 135 mmHg. However for stroke, where the intensive arm demonstrated benefit, the magnitude of benefit was greater in trials where the achieved systolic BP was <130 mmHg as compared to those where the achieved systolic blood pressure was between 130 and 135 mmHg.[168] Putting the evidence in perspective, for people with type 2 diabetes, a systolic blood pressure range of between 130-139 mmHg is acceptable. Where there is reason to believe that a particular patient has a greater propensity for ischaemic stroke rather than for other cardiovascular outcomes, a lower systolic blood pressure target may be discussed. However, the possibility of having more adverse events with a lower blood pressure target should also be considered. Lower systolic blood pressure targets may also be appropriate in younger patients who are at low risk of suffering from the adverse consequences of achieving these targets.

There is a paucity of evidence to provide guidance on management of hypertension in the elderly, particularly in those older than 80 years. The active arm of the Hyvet study (mean age 83.5 years, including 6.8% of subjects with diabetes), attained a blood pressure of 143.5/77.9 mmHg after about 2 years and had lower stroke rates as well as overall and cardiovascular mortality rates when compared to the control arm with a mean blood pressure of 158.5/84 mmHg.[176] Hence more conservative treatment targets which are higher than 130/80 mmHg may be appropriate in the very elderly where life expectancy and quality of life may be limited. A recent AHA/ACCF consensus document on management of hypertension in the elderly has suggested that in people older than 80 years, systolic blood pressure of 140-145 mmHg may be acceptable.[177]

There has been recent rethinking about diastolic blood pressure.[178] Diastolic blood pressure tends to fall progressively after age of 50 years even as systolic blood pressure rises. This may be a function of the decreasing distensibility of major arteries with increasing age. Hence low diastolic blood pressure may reflect cardiovascular risks accrued from risks and co-morbidities associated with poorly distensible arteries and ageing. Secondly, from a theoretical perspective, coronary perfusion occurs to a major extent during diastole, and an excessively low diastolic blood pressure may lead to suboptimal coronary perfusion particularly in patients with diseased coronary vessels.

A recent sub study which performed epidemiologic analysis form the INVEST study demonstrated that the hazard ratio nadir diastolic blood pressure for primary as well as secondary outcomes across age groups was between 70-80 mmHg.[170] Similarly, an analysis of both baseline and on-study blood pressure of the VADT study subjects revealed an increased risk for the primary composite cardiovascular end point in patients with a diastolic blood pressure category lower than that of 70-79 mmHg.[169] Hence, for most patients with type 2 diabetes, an acceptable target diastolic blood pressure range is 70-80 mmHg. The patients with isolated systolic hypertension with diastolic blood pressure near the lower bound of the suggested diastolic blood pressure range should be managed judiciously and antihypertensive therapy should be started in small doses with close monitoring. While the benefits of lowering high systolic blood pressure are discussed, the potential harm of lowering diastolic blood pressure further should also be considered particularly in the presence of pre-existing coronary disease.[179]

7.9 Choice of pharmacologic therapy

B An angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) should be included as part of antihypertensive regimen for people with type 2 diabetes requiring pharmacotherapy for hypertension, unless not well tolerated.[180-183]

Grade B, Level 2+

There are six 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
(e) angiotensin receptor blockers (ARB)
(f) renin inhibitors (RI)

Less commonly used agents include alpha blockers, methyldopa and hydralazine.

Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not well tolerated, the other should be substituted. ACE inhibitors and ARBs have been shown in earlier trials to be beneficial in terms of reducing incident microalbuminuria and as well as in retarding progression of diabetic nephropathy.[181-184] In the more recent ADVANCE BP trial, where an ACE inhibitor and diuretic combination was used, the relative risk of the primary composite endpoint of both macrovascular and microvascular outcomes as well as total mortality and cardiovascular mortality were reduced when compared to the placebo arm although the advantage might be deemed to have been accrued partially by difference in BP attained between the active treatment and the placebo arms.[173] In the ACCOMPLISH trial, of which 60% of study subjects were people with diabetes, the combination of ACE inhibitor and CCB (benazepril and amlodipine) conferred a risk reduction in the composite end point of cardiovascular death, nonfatal myocardial infarct, nonfatal stroke when compared to the combination of ACE inhibitor and diuretic (benazepril and hydrochlorthiazide).[185] Both these trials involved use of ACE inhibitors. The ACCOMPLISH trial may also be viewed as possibly providing data which may provide guidance for selection of a second antihypertensive agent.

Besides these considerations, the choice of antihypertensive agents in people with diabetes should also look into whether there are compelling indications or possible contraindications.

Table 7 Guidelines for selecting drug treatment of hypertension[186]

Concomitant Conditions	Recommended Drugs	Contraindicated Drugs
Heart Failure	• diuretics • ACE inhibitors • angiotensin receptor blockers	• calcium channel blockers
Angina	• beta-blockers • calcium channel blockers	-
Post Myocardial Infarction	• beta-blockers • ACE inhibitors • angiotensin receptor blockers	-
Isolated Systolic Hypertension	• diuretics • calcium channel blockers • ACE inhibitors • angiotensin receptor blockers	-
Diabetes Mellitus with Proteinuria (micro or Macroalbuminuria)	• ACE inhibitors • angiotensin receptor blockers	-
Diabetes Mellitus	• ACE inhibitors • angiotensin receptor blockers • calcium channel blockers • diuretics • beta-blockers	-
Post-Stroke	• diuretics • ACE inhibitors	-
Asthma & Chronic Obstructive Pulmonary Disease	-	• beta-blockers
Heart Block	-	• beta-blockers • calcium channel blockers
Gout	-	• diuretics
Bilateral Renal Artery Stenosis	-	• ACE inhibitors • angiotensin receptor blockers

[*] *verapamil or diltiazem*

(Source: MOH Clinical Practice Guidelines 2/2005 Hypertension, Table 6, p27)

7.10 Management of dyslipidaemia in persons with type 2 diabetes mellitus

D All persons with type 2 diabetes mellitus should have a full lipid profile, including low density lipoprotein (LDL) cholesterol, fasting triglyceride and low density lipoprotein (HDL) cholesterol, measured at the time of diagnosis. These should be obtained after 10-12 hours of fasting.[105]

Grade D, Level 4

D If optimal, serum lipids should be measured 12-monthly in persons with type 2 diabetes.[105]

Grade D, Level 4

7.11 Goals of therapy in the management of dyslipidaemia

In the management of dyslipidaemia for the prevention of CHD, the first priority is optimization of LDL cholesterol.[187]

D The majority of patients with type 2 diabetes mellitus should have a primary low density lipoprotein (LDL) cholesterol goal <2.6 mmol/L and should receive medical nutrition and pharmacological therapy to achieve this goal.[105]

Grade D, Level 4

D Patients with diabetes who have overt cardiovascular disease and / or chronic kidney disease but are not on maintenance haemodialysis should have low density lipoprotein (LDL) cholesterol lowered with combination of dietary and pharmacological means to a target of <2.1 mmol/L.[184, 187]

Grade D, Level 4

D When making a therapeutic decision with the patient, the potential benefits of adding/increasing lipid-lowering pharmacological treatment needs to be considered together with the potential risks of such treatment.[188]

Grade D, Level 4

7.12 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. However where the lipid panel is performed in a laboratory where the LDL cholesterol is calculated using the Friedewald formula, triglyceride of >4.5 mmol/L should be brought down by dietary and/or pharmacological means before the LDL cholesterol is estimated. Individuals with levels of TG >10 mmol/L (approximately 900 mg/dl) have an increased risk of acute pancreatitis. In these patients, the TG is reduced to prevent acute pancreatitis before turning attention to LDL cholesterol lowering. In patients where a fibrate is used in combination with a statin, gemfibrozil should not be used.[189]

7.13 Choice of pharmacologic therapy

D For most patients with type 2 diabetes mellitus where low density lipoprotein (LDL) cholesterol is >2.6 mmol/L, an HMG CoA reductase inhibitor (statin) should be started concurrently with therapeutic lifestyle modification.[187]

Grade D, Level 4

The beneficial effects of LDL cholesterol lowering and the utility of statins in LDL cholesterol lowering in people with diabetes is now well established. [187, 190]

The results of the VA-HIT study suggest that patients with established CHD whose primary lipid abnormality is a low HDL cholesterol despite lifestyle changes, can be offered a fibrate to elevate the HDL-cholesterol level.[191] However, the FIELD study, which looked at the effects of long-term fenofibrate treatment to raise HDL-cholesterol and lower triglyceride levels in patients with type 2 diabetes did not show significant reduction in the risk of primary outcome of coronary artery events.[192] This generally reduced the enthusiasm for the use of fibrate in triglyceride-lowering in patients with type 2 diabetes.

In the ACCORD lipid lowering study, addition of fenofibrate to simvastatin also did not decrease the rate of primary outcome when compared to simvastatin alone. However in subgroup analysis, subjects with high triglyceride (>2.3 mmol/L) and low HDL cholesterol (<0.88

mmol/L) appeared to have a possible benefit. Hence the option of adding a fibrate to patients who have such a pattern of dyslipidaemia while on statin therapy may be considered.[193]

The Arbiter 6 study (of which 32-40% of study subjects were people with diabetes) demonstrated that in patients treated with statins, the addition of niacin resulted in significant reduction of carotid intima media thickness when compared to addition of ezetimibe. This result lent support to the notion that elevation of HDL cholesterol after initial control of LDL cholesterol was superior to further reduction in LDL cholesterol.[194] However the unexpected early termination of the Aim-High study recently has created much uncertainty regarding the use of niacin. In this study, high-dose extended-release niacin was given in addition to statin therapy to patients with a history of cardiovascular disease, high triglycerides, very well controlled LDL cholesterol levels and low levels of HDL cholesterol. The study was terminated early because niacin was thought to offer no additional benefits in this patient population.[195] It is unclear at the moment whether these findings would extend to subjects with different characteristics who are on niacin. The preliminary results of the HPS2-THRIVE study which uses extended release niacin with laropiprant revealed that the combination of extended release niacin and laropiprant in addition to statin therapy did not significantly further reduce the risk of the combination of coronary deaths, non-fatal heart attacks, strokes or revascularizations. In addition, there was a statistically significant increase in the incidence of some types of non-fatal serious adverse events in the group that received extended release niacin/laropiprant including myopathy amongst Chinese subjects.[196]

7.14 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 cardiovascular disease. Antiplatelet agents, such as aspirin, have been used, particularly in the secondary prevention setting, to reduce risk of recurrent cardiovascular events. However, use of aspirin in primary prevention in people with diabetes has recently undergone re-consideration. In the recent POPADAD study, which exclusively studied people with diabetes, and had an ankle brachial index of 0.99, those who were started on aspirin did

not fare better in primary composite cardiovascular endpoint when compared to those who were not.[14] Similarly, the JPAD study which enrolled 2,539 Japanese patients with diabetes but without history of previous athersosclerotic disease, failed to establish a statistically significant benefit in reduction of cardiovascular events in those treated with low dose aspirin.[161] Hence the age of initiation at which aspirin is recommended for primary prevention is now pushed back to 50 years for males and 60 for females, provided patients also have at least an additional cardiovascular risk factor.

D It is reasonable to initiate low dose aspirin for primary prevention in people with diabetes and no previous history of vascular disease at age 50 years for men, and 60 years for women, provided they also have at least one more of the following cardiovascular risk factors: smoking, hypertension, dyslipidaemia, family history of premature cardiovascular disease and albuminuria.

Grade D, Level 4

Low dose (75–162 mg/day) aspirin use for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease, who are at increased cardiovascular disease risk (10-year risk of cardiovascular disease events over 10%) and who are not at increased risk for bleeding. This generally includes men over age 50 years and women over age 60 years who also have one or more of the following major risk factors besides having diabetes: smoking, hypertension, dyslipidemia, family history of premature cardiovascular disease, and albuminuria.[182]

GPP 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.

GPP

7.15 Prevention of cardiovascular disease in people with type 1 diabetes mellitus

A Norwegian study on people with type 1 diabetes mellitus (mean age 43 years) revealed that silent coronary atherosclerosis was present in 34% of subjects.[197] The risk factors for cardiovascular disease for people with type 1 diabetes are similar to those with type 2 diabetes.

In addition, as in type 2 diabetes, intensive glucose control has been shown in the DCCT/EDIC study to improve cardiovascular outcomes many years later, even as intensive control wanes.[18] However, at the same time, meticulous care to avoid hypoglycaemia is needed, as the dead-in-bed syndrome seen occasionally in patients with type 1 diabetes has been thought to be related to cardiac arrhythmias and conduction abnormalities associated with nocturnal hypoglycaemia.[198]

8 Diabetic nephropathy – screening and treatment

8.1 Introduction

In Singapore, diabetic nephropathy is an important cause of chronic kidney disease (CKD), accounting for ~47% of incident end stage renal disease (ESRD) requiring renal replacement therapy.[199] It is estimated that 20-40% of diabetic individuals will end up with CKD. Diabetic nephropathy is also associated with substantial increase risk for cardiovascular disease (CVD).[200]

Considerable heterogeneity exists in the natural history of diabetic nephropathy.[201] In general, diabetic subjects develop micro-albuminuria initially. This may lead to macro-albuminuria, diminished glomerular filtration rate (GFR) and eventually ESRD. The order of these events may not be sequential. For instance, it is possible for micro-albuminuria to be followed by diminished GFR without macro-albuminuria.[202] Therefore, diabetic nephropathy screening should also include measurement of serum creatinine to assess GFR.

Screening

Albuminuria

D It is recommended to perform an annual test to assess urine albumin excretion in type 1 diabetic patients with diabetes duration of 5 years and in all type 2 diabetic patients, starting at diagnosis.[105]

Grade D, Level 4

Several methods are available. However, the most widely recommended method is albumin-specific detection with correction for urinary creatinine (i.e. albumin/creatinine ratio) in a freshly collected,[203] random spot urine sample.[50] Factors other than diabetic nephropathy are associated with micro-albumuria e.g., febrile illness, heavy physical exertion, severe uncontrolled diabetes and congestive cardiac failure. Therefore, two to three samples collected within 3 – 6 months should be abnormal to classify an individual as having abnormal albuminuria. Classification of severity of albuminuria is as shown in Table 8.

Table 8 Definition of albuminuria* [204-205]

	Spot collection	
	(µg/mg)	(mg/mM)
Normal	<30	<3.3
Micro-albuminuria	30-299	3.4-33.9
Macro-albumniuria	>300	>33.9

(Adapted from: American Diabetes Association. Preconception care of women with diabetes. Diabetes Care. 2003; Jacobs DR et al. Am J Epidemiol. 2002)

* Some experts recommend gender adjusted threshold to classify albuminuria.[105]

Epidemiological data suggested that gender and race differences in creatinine excretion may bias the estimate of albumin/creatinine ratio.[205] However, diabetic nephropathy clinical management strategies based on these gender and ethnic specific diagnostic thresholds have not been rigorously tested.

When albuminuria is heavy (≥ 300 mg/g or 33.9 mg/mM), some clinicians adopt the non-albumin specific measurement of urinary protein/creatinine ratio (PCR) to monitor the progress of renal function and effectiveness of interventions. Measuring urinary total protein (instead of albumin-specific measurement) has the advantage of better assay dynamic range (at high protein concentration) and wide availability.

8.2 Assessment of glomerular filtration rate

Measure serum creatinine at least annually in all adults with diabetes (regardless of the degree of urine albumin excretion) is recommended. The serum creatinine should be used to estimate GFR and stage the level of CKD, if present.

D Measure serum creatinine at least annually in all adults with diabetes (regardless of the degree of urine albumin excretion) is recommended. The serum creatinine should be used to estimate glomerular filtration rate (GFR) and stage the level of chronic kidney disease (CKD), if present.[105]

Grade D, Level 4

Serum creatinine, measured using a validated laboratory method, should be used to estimate GFR (eGFR) and to stage the level of CKD, if present (Table 9). The Modification of Diet in Renal Disease (MDRD) study equation is recommended for the derivation of eGFR. GFR calculators are available at http://www.nkdep.nih.gov. The parameters required are age, gender and serum creatinine level. MDRD equation does not perform well when GFR is >60 mls/min/1.73m^2.[206] Therefore, it is only recommended to estimate renal function when eGFR is below 60 mls/min/1.73m^2.

Table 9 Stages of chronic kidney disease[207]

Stage	Description	GFR(ml.min/1.73 m^2)
1 & 2	Kidney damage* with normal or mildly decreased GFR	>60**
3a	Mild - Moderately decreased GFR	45-59
3b	Moderately-severe decreased GFR	30-44
4	Severely decreased GFR	15-29
5	Kidney failure	<15 or dialysis

(Adapted from: Levey AS, Coresh J. Lancet. 2012)

* Kidney damage refers to abnormalities on pathologic, urine, blood or imaging tests.
** GFR estimation using MDRD formula is considered insufficiently accurate when actual GFR is > 60 ml.min/1.73 m^2

C It is only recommended to estimate renal function with the Modification of Diet in Renal Disease (MDRD) equation when eGFR is below 60 mls/min/1.73m^2.[208]

Grade C, Level 2$^+$

Investigators have tried to improve on the MDRD formula e.g., the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[209] However, it is unclear whether the new CKD-EPI formula will perform better than the MDRD formula in the diabetic population.[210] Asian-specific coefficients have also been proposed to adjust eGFR derived from original MDRD formula. However, these ethnic-specific adjustments have not been well validated.[211]

8.3 Treatment

Optimised blood glucose and blood pressure (BP) control have been shown to reduce the risk or slow the progression of diabetic nephropathy. There is also synergistic efficacy between blood glucose and blood pressure control.[14]

Glycaemic control

Several large scale landmark clinical randomised control trials have consistently demonstrated the benefit of glycaemic control and incident nephropathy (defined as progression of albuminuria and/or worsening of serum creatinine) [21,25-26,212] However, it appears prudent to avoid over-zealous intensification of blood glucose control (i.e. rapidly achieving glycated haemoglobin level below 6%) in diabetic nephropathy patients who are also at risk for CVD.[213] In addition, it is advisable to consider need for dose adjustment of medications in the presence of CKD.[214-215] For the adjustment of diabetic pharmacotherapy in presence of renal impairment, please refer to Chapter 5.

A To reduce the risk or slow the progression of nephropathy, optimised glucose control is recommended.

Grade A, Level 1+

8.4 Blood pressure control

Several large scale land mark clinical randomised control trials have consistently demonstrated the benefit of BP lowering and incident nephropathy (defined as progression of albuminuria and/or worsening of serum creatinine).[28, 173, 216] A target blood pressure of 130/80 mmHg appears reasonable.[217-218] The benefit of further blood pressure lowering is unproven and may potentially be hazardous in individuals with pre-existing coronary artery disease.[174-175, 219-220] To reduce the risk or slow the progression of nephropathy, optimised blood pressure control is recommended.

A To reduce the risk or slow the progression of nephropathy, optimised blood pressure control is recommended.

Grade A, Level 1+

Blockade of the rennin-angiotensin-aldosterone system using angiotensin-converting enzyme (ACE) inhibitor[221] or angiotensin receptor blocker[182, 222] (ARB) has been shown to reduce the risk or slow the progression of diabetic nephropathy.[223] Therefore, it is recommended that in the treatment of the non-pregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.

A It is recommended that in the treatment of the non-pregnant patient with micro- or macroalbuminuria, either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be used.[182, 221-223]

Grade A, Level 1+

While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following three circumstances:

A In patients with type 1 diabetes, with hypertension and any degree of albuminuria, angiotensin-converting enzyme (ACE) inhibitors are recommended.[221]

Grade A, Level 1+

A In patients with type 2 diabetes, hypertension, and microalbuminuria, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are recommended.[182, 222]

Grade A, Level 1+

A In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), angiotensin receptor blockers (ARBs) are recommended.[182, 222]

Grade A, Level 1+

D In patients with diabetes, if one class [either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)] is not tolerated, the other should be substituted.

Grade D, Level 4

ACE inhibitor and ARB combination can further reduce proteinuria.[224] However, there is insufficient data from clinical randomised control trial to routinely recommend this combination for the purpose of renal retardation.[225] When ACE inhibitors, ARBs, or diuretics are used, it is recommended to monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia.

A few evolving therapeutic agents have shown promise in anti-proteinuria or renal retardation. These include rennin antagonist,[226] aldosterone receptor antagonist,[227] fibrates,[228] vitamin-D analogue[229] and bardoxolone methyl.[230] However, confirmatory large scale clinical studies are awaited. When diuretics, ACE inhibitors or ARBs are used, monitor serum sodium, potassium and creatinine levels for the development of hyponatremia, hyperkalemia and acute kidney disease.

D When angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or diuretics are used, it is recommended to monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia.

Grade D, Level 4

Lipids management

Optimising blood lipids (especially with statins) may be modestly helpful in retarding progression of renal impairment.[231] More importantly, lipid lowering therapy also helps to reduce the cardiovascular burden in diabetic nephropathy. A recent landmark clinical trial suggested that LDL-cholesterol lowering could safely reduce the incidence of major atherosclerotic events in CKD.[184] Therefore, lipids management in diabetic nephropathy should adhere to existing guidelines recommended for diabetic individuals.

A To reduce the risk or slow the progression of nephropathy, optimised lipid control is recommended.

Grade A, Level 1+

Protein restriction

A Reduction of protein intake to 0.8–1.0 g per kg body wt per day in individuals with diabetes and earlier stages of chronic kidney disease (CKD) and to 0.8 g per kg body wt per day in the later stages of CKD is recommended to improve measures of renal function (urine albumin excretion rate, GFR).[232-233]

Grade A, Level 1+

Anti-platelet therapy

Aspirin is recommended for the prevention of CVD in patients with a history of vascular disease (secondary prevention). In contrast, the efficacy of aspirin in the primary prevention of CVD among diabetic individuals is less established.[234] Nevertheless, subgroup analysis from one large Asian clinical trial suggested that mild diabetic nephropathy (eGFR 60–89 mL/min/1.73 m^2) may benefit from aspirin.[235] Therefore, it appears reasonable to consider low-dose aspirin in diabetic individuals with significant cardiovascular burden (e.g., estimated 10 year risk of CVD >10%).[236] It is recommended to consider low-dose aspirin in diabetic individuals with history of vascular disease or who carry a significant cardiovascular risk burden.

A It is recommended to consider a low-dose aspirin in diabetic individuals with a history of vascular disease.

Grade A, Level 1+

D It is recommended to consider low-dose aspirin in diabetic individuals who carry significant cardiovascular risk burden.

Grade D, Level 4

Monitoring

Continual monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended. Although not rigorously tested in clinical trials, substantial reduction in albuminuria (e.g., 50% reduction of the pre-intervention value) is considered a desirable therapeutic goal. When estimated GFR (eGFR) is <60 ml.min/1.73 m^2, evaluate and manage potential complications of CKD. These include anemia, CKD-metabolic bone disease and hyper-uricemia.[237]

D Continual monitoring of urine albumin excretion to assess both response to therapy and progression of disease is recommended for both type 1 and type 2 diabetes patients.

Grade D, Level 4

D It is recommended that when estimated GFR (eGFR) is <60 ml.min/1.73 m^2, evaluate and manage potential complications of chronic kidney disease.

Grade D, Level 4

Referral to specialist

It is recommended to consider referral to a physician experienced in the care of kidney disease when there is:

1) uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR),
2) difficult management issues (blood pressure, hyperkalemia control),
3) advanced kidney disease.

D It is recommended to consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease.[105]

Grade D, Level 4

9 Prevention and management of eye complications

9.1 Introduction

Diabetic retinopathy is a major blinding eye disease. About a third of people with diabetes have signs of diabetic retinopathy, and a tenth of these might have vision-threatening retinopathy, defined as severe retinopathy or macular oedema.[238] Currently, an estimated 2.5 million people worldwide are blind from diabetic retinopathy.[239] Persons with diabetes are 25 times more likely to become blind compared to persons without diabetes. [240]

There is increasing local data on the prevalence and risk factors for diabetic retinopathy in Singapore. Studies show that retinal conditions including diabetic retinopathy is a leading cause of blindness in adults.[241] 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% had sight-threatening retinopathy.[242] Recent data from the local Malay community have found that 34% of adult diabetic subjects had diabetic retinopathy, with 10% having vision threatening retinopathy.[243] The prevalence of diabetic retinopathy is similar amongst the three racial groups in Singapore: Chinese, Malays and Indians.[244]

9.2 Screening and methodology

There continues to be low awareness of diabetic retinopathy amongst people with diabetes in Singapore.[245] The early detection of potentially sight-threatening diabetic retinopathy in often asymptomatic patients is the key to reducing blindness from diabetic retinopathy. Thus, screening for diabetic retinopathy is important.

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

Direct ophthalmoscopy and retinal (fundus) photography are the two common methods of screening available to primary healthcare practitioners. For better outcomes, the retinal 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 diabetic macular edema in all cases.[246]

There is good evidence that retinal (fundus) photography can serve as a screening tool for the detection and evaluation of diabetic retinopathy.[247] Retinal photography is preferred to direct ophthalmoscopy as the later has limited and narrow field of view, is difficult to perform in the presence of poorly dilating pupils and/or cataracts,[248] and lacks a hard documentation 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.[249]

While there is debate on the exact method on retinal screening, some studies show that a single-field retinal photography and assessment by specially trained and certified non-physician graders (NPGs) is comparable to dilated fundus examination by an ophthalmologist for assessing diabetic retinopathy, with a high sensitivity (61–90%) and specificity (85–97%).[247, 250-253]

D 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 D, Level 4

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

Grade D, Level 4

9.3 Eye examination and minimum follow-up schedule

Table 10 Eye examination schedule[254-255]

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

(Adapted from: Klein et al. Arch Ophthalmol. 1984)

D Type 1 diabetic patients should have an eye examination 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 D, Level 4

D Women with diabetes mellitus who intend to have children should preferably have an eye examination prior to conception, followed by one during the early first trimester. Further eye examinations during pregnancy may be done depending on the results of the first trimester examination.

Grade D, Level 4

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

The implications of these risk factors are summarised in Table 11.

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[26]
Hypertension	10 mmHg reduction in blood pressure	13% reduction in risk of diabetic retinopathy[28]
Hyperlipidaemia	Treatment of hyperlipidaemia, particularly with fenofibrate	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

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.[254] 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.[255]

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% or 53 mmol/mol) reduces the overall incidence of microvascular complications (including diabetic retinopathy) by 25% compared to conventional treatment (median HbA_{1c} level 7.9% or 62.8 mmol/mol).[26, 256]

A reduction in the mean HbA_{1c} by 0.9% (from 7.9 to 7.0% or 62.8 to 53 mmol/mol) translates into a corresponding reduction in the risk of microvascular complications (including retinopathy) by 37%.[163]

Similar results were reported in an Asian population.[257] In type 1 diabetic patients intensive glycaemic control reduces the risk of diabetic retinopathy by 50-75%.[25] Conversely, poor glycaemic control (HbA_{1c} > 10% or 85.8 mmol/mol) in type 1 diabetic patients increases the risk of developing retinopathy by eight times.[258] 53.2% of diabetics in the National Health Survey had poor blood glucose control with a mean HbA_{1c} of 8.5% or 69.4 mmol/mol.[259] A meta-analysis of three large population based studies showed a continuous reduction in the prevalence of retinopathy with lower levels of glycemia.[260] However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has also shown that intensive control with a target HbA_{1c} of <6.0% or 42.1 mmol/mol or may be associated with increased mortality.[24]

A Good glycaemic control (HbA_{1c} preferably 6.5 to 7.5% or 47.5 to 58.5 mmol/mol) should be instituted to reduce the risk and progression of diabetic retinopathy.

Grade A, Level 1+

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.[261]

Retinal assessment should be carried out before initiation of intensive insulin therapy and then at 3-monthly intervals for 6-12 months.

D Rapid normalisation of blood glucose may worsen retinopathy and thus retinal assessment should be carried out before initiation of intensive insulin therapy and then at 3-monthly intervals for 6-12 months. Patients should be carefully monitored during this period.

Grade D, Level 3

Hypertension

Hypertension is a known risk factor for progression of diabetic retinopathy.[256] 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.[28] Microvascular end-points including retinopathy are decreased by 13% with each 10 mmHg reduction in the systolic blood pressure.[262] Blood pressure control with drugs targeting the rennin-angiotensin pathway may lower the retinopathy risk additionally.[263-265]

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

Grade A, Level 1+

Dyslipidaemia

The prevalence of diabetic retinopathy is positively associated with increased cholesterol and triglyceride levels.[266] 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.[267]

There is a possibility that treatment of associated hyperlipidaemia may retard diabetic retinopathy. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial has shown that fenofibrate reduces the need for laser treatment of vision-threatening diabetic retinopathy by 31% in patients with type 2 diabetes,[268] while the ACCORD study has shown that adding fenofibrate to patients already on statins reduces the risk of diabetic retinopathy progression by 40%.[24]

B Significant hyperlipidaemia should be treated to retard diabetic retinopathy. Consideration should be given to using fenofibrate.

Grade B, Level 1+

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.[269] 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.[270] 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.[271]

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.[272]

Anaemia

Normocytic anaemia is associated with an increased risk of diabetic retinopathy, especially the severe form.[273] Concurrent treatment of anaemia may possibly slow the progression of diabetic retinopathy.[274]

9.5 Classification of diabetic retinopathy

The International Clinical Diabetic Retinopathy Disease Severity Scale and Diabetic Macular Oedema Severity Scale[275] arose out of the need for a unified and global classification that would facilitate communication amongst diabetes care-givers (refer to Tables 12 and 13). The presence and severity of diabetic retinopathy and diabetic macular oedema should be assessed separately. While there is a good correlation of severity of retinopathy with macular oedema, patients with mild diabetic retinopathy may have diabetic macular oedema; conversely, patients with severe diabetic retinopathy may not have macular oedema.

Table 12 International Clinical Classification of Diabetic Retinopathy[275]

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

(Source: Wilkinson CP et al. Ophthalmology. 2003. Table 2, p1679)

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

Table 13 Diabetic macular oedema severity scale[275]

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

(Source: Wilkinson CP et al. Ophthalmology. 2003. Table 3, p1680)

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

9.6 Referral for ophthalmologic opinion

1. Diabetic macular oedema
2. Moderate or severe non-proliferative diabetic retinopathy
3. Unexplained drop in visual acuity
4. Unexplained eye findings

Earlier referrals

1. Proliferative diabetic retinopathy
2. Pre-retinal / vitreous haemorrhage
3. Rubeosis iridis (new vessels on the iris)

Urgent referrals

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

GPP Diabetic patients found to have diabetic macular oedema or moderate and more severe non-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.[276-277]

Grade A, Level 1+

Panretinal and focal/grid laser treatment results in at least a 50% reduction in the risk of visual loss.

Visual acuity testing

There is broad expert consensus that examination of visual acuity is an essential element of the overall approach to eye care for people with diabetes and is therefore an important part of clinical practice.

A visual acuity of 6/18 or worse is recommended as a cut off for referral.

Diabetic macular oedema is an important complication of diabetes leading to reduced visual acuity if untreated. Because of the difficulty of determining the difference between non-significant diabetic macular oedema and clinically significant diabetic macular oedema, the national screening committee, UK panel recommends that visual acuity testing be used as a screening test for this complication in routine practice. Reduced visual acuity is an indication for specialist referral. While there may be other causes of a drop in visual acuity, the prospect of unmanaged diabetic macular oedema alone is a reason for considering its value. Thus both the UK and the Australian diabetic retinopathy screening programmes recommend visual acuity testing for all the patients screened.

Harding et al[278], in their study concluded that measuring visual acuity alongside retinal photography increased sensitivity of photography from 89% to 91%. For direct ophthalmoscopy measuring visual acuity increased sensitivity from 65% to 74%.

GPP Diabetic patients with visual acuity of 6/18 or worse or with diabetic macular oedema should be referred for further ophthalmological assessment.

GPP

9.7 Treatment

Aspirin and other systemic medications

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.[256, 279]

No protective effect on diabetic retinopathy has been found with the use of antioxidants.[280] The routine use of aldose reductase inhibitors and growth hormone suppression for the sole purpose of reducing the progression of diabetic retinopathy is also not supported by available evidence.[256]

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.[238,256,280] 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 therefore 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.[276] Laser treatment (focal/grid) for diabetic macular oedema (maculopathy) is also effective with a similar reduction in visual loss rate (50%). [277]

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

Grade A, Level 1+

A Focal/grid laser photocoagulation should be instituted for diabetic macular oedema as it results in a 50% reduction in risk for moderate visual loss.

Grade A, Level 1+

Intravitreal anti-VEGF injections

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents (e.g., ranibizumab, bevacizumab) have been used for diabetic macular edema as well as diabetic retinopathy.[238] There are now several multi-centered randomised trials that have shown anti-VEGF agents are useful in preventing visual loss, improving mean visual acuity and in reduction in macular oedema.[281-285] The DRCR.net group has evaluated the effect of ranibizumab on diabetic macular edema in a phase III randomised trial. The trial compared laser therapy plus intravitreal ranibizumab injections versus laser therapy plus sham injections. Over the first year, subjects in the ranibizumab group experienced approximately one-line extra vision gained over laser therapy. Improvement of vision was twice as frequent in the ranibizumab group (50% for two-line and 30% for three lines or more) as in the laser group (28% and 15%). Eyes treated with laser and ranibizumab (3–4%) were less likely to have marked visual loss than those treated with laser therapy alone (13%). Intravitreal anti-VEGF injections have also been reported anecdotally to control proliferative diabetic retinopathy as well.[283]

There have been numerous reports on serious systemic side effects of anti-VEGF agents including stroke, myocardial infarction, although the incidence is generally low. More definitive safety data is however lacking and caution and vigilance are needed with the use of these agents.

A Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents may be offered to patients with diabetic macular oedema, particularly in cases where laser photocoagulation has not been effective.

Grade A, Level 1+

Intravitreal steroid injections

Intravitreal injections of steroids have also been used for treatment of diabetic macular edema.[238] However, the evidence for its use has been conflicting.[238,283] Its routine use for diabetic macular edema is therefore currently not recommended

Vitreous surgery/vitrectomy

Vitreous surgery (vitrectomy) is sometimes indicated in patients with advanced proliferative diabetic retinopathy, such as vitreous haemorrhage and/or traction detachment involving the macula. In particular, early vitrectomy has also been shown to be beneficial in type 1 patients with dense vitreous haemorrhage.[286]

B Vitrectomy may be offered to selected patients with advanced diabetic retinopathy.

Grade B, Level 1+

Table 14 Management and stage of diabetic retinopathy

Stage/Severity	Relative Risk of Progression	General Management	Eye Examination Frequency	Eye Treatment
No retinopathy	-	Optimisation of blood glucose, blood pressure and lipids	12 monthly	None
Mild Non-Proliferative Diabetic Retinopathy	-	Optimisation of blood glucose, blood pressure and lipids	6-12 monthly	None
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	-
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 may increase risks	Close follow-up	Pan-retinal laser photocoagulation may be indicated in certain scenarios (e.g., if patient is not compliant with close follow-up, in eyes prior to cataract operation, or pregnancy and in patients that has advanced retinopathy or blindness in fellow eye).
Proliferative Diabetic Retinopathy	-	Manage systemic risk factors Rapid normalisation of blood glucose prior to laser may increase risks	Close follow-up	Pan-retinal laser photocoagulation. Consider use of intravitreal anti-VEGF injections

Stage/Severity	Relative Risk of Progression	General Management	Eye Examination Frequency	Eye Treatment
Vitreous / Preretinal Haemorrhage Neovascular Glaucoma	-	Manage systemic risk factors	Close follow-up	Pan-retinal photocoagulation (if clear media allows laser) Lower intraocular pressure by medical means Consider various non-surgical / surgical options, where appropriate (e.g., intravitreal anti-VEGF injections or vitrectomy)
Diabetic Macula Edema	-	Manage systemic risks factors	Close follow-up	Focal/grid laser photocoagulation for moderate and severe diabetic macular edema Intravitreal anti-VEGF injections for diabetic macular edema

(Adapted and based on: 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 susceptibility to corneal abrasions with slower recovery, decreased corneal sensation)
2. Cataracts
3. Optic neuropathies (acute ischemic optic neuropathy, diabetic papillopathy)
4. Cranial neuropathies (third, fourth and sixth cranial neuropathies)
5. Glaucoma (primary glaucoma and neovascular glaucoma)
6. Orbital fungal infection (mucormycosis)

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.[287] In Singapore, approximately 700 lower extremity amputations are performed in diabetic patients annually.[288] Foot complications affect not only the individual but also the country in terms of productivity and costs. The estimated costs of a lower extremity amputation in the USA is US$12,230 to US$40,563[289] (per individual) and US$709,000,000 for the country (annually).[290]

10.2 Screening

Studies show that a systematic screening, treatment and patient education protocol can reduce the lower extremity amputation rate by 44-85%.[291-292] Risk identification is fundamental for effective preventive management of the foot in people with diabetes.[287]

10.3 Risk identification

B All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions.[287]

Grade B, Level 2+

B The assessment of the feet involves risk identification, treatment and patient education appropriate to the level of risk.[291-292]

Grade B, Level 2+

GPP All patients, regardless of risk category, should receive ongoing education on footcare and footwear advice.

GPP

The following foot-related risk conditions are associated with an increased risk of amputation (see Table 15).

Table 15 Diabetic foot-related risk conditions

Description	Signs & Symptoms
Ulceration or prior lower extremity amputation	• History of ulceration • History of lower extremity amputation
Peripheral neuropathy	• Presence of paraesthesia or anaesthesia • Negative tuning fork 128Hz (vibratory perception threshold) sensation • Biothesiometer / Neurothesiometer sensation at ≥ 25 volts • Negative monofilament* sensation • Negative pin prick sensation • Clawed toes • Very dry feet
Peripheral vascular disease	• Intermittent claudication/rest pain • Absent pedal pulses • Absence of hair • Absence of gradual temperature gradient • Positive Buerger's test
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", clogs • 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.[287] For those at high risk of foot pathology, a referral to the community or hospital specialist footcare team should be considered.[293]

10.4 Footcare protocol

C Patients identified with foot-related risk conditions should have access to a specialised footcare team which should include diabetes specialist, podiatrist, physiotherapist trained in diabetes, diabetes nurse educator, vascular and orthopaedic surgeons.

Grade C, Level 3

Table 16 Footcare protocol[294]

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	• DM footcare education/footwear advice • Wound debridement and management • Custom made orthosis/insoles for pressure redistribution • Footwear adaptations • Surgical interventions such as vascular stenting or bypass, contact casting, osteotomy and internal fixation when necessary	• Regular interval as clinically indicated • Frequent reinforcement

(Adapted from: National evidence-based guideline on prevention, identification and management of foot complications in diabetes Melbourne, Australia: Commonwealth of Australia. 2011)

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
d) Surgical Interventions

10.5.1 Mechanical control

Mechanical control involves wearing the correct footwear (refer to Table 18, page 130) and the diagnosis and treatment of common foot problems.

10.5.2 Metabolic control

Optimisation of glycaemic control and other cardiovascular risk factors is important. Smoking cessation should be encouraged to reduce the risk of vascular disease complications. For patients with pre-existing vascular disease, they should be encouraged to do walking exercise, and an anti-platelet agent should be started.

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.[295] 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, diabetes foot screening nurse or diabetes nurse educator. Being well informed and motivated is the best defense against diabetic limb loss.[296]

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

10.5.4 Surgical interventions

a) In the absence of well-felt pedal pulses, the presence of lower limb rest pain or any tissue loss, such as ulceration or gangrene, warrants an urgent review by a vascular surgeon within one to two weeks, as early re-vascularisation may be required.

GPP Urgent referral to a specialised footcare team is needed in the presence of ulcerations, severe foot infection and gangrene.

GPP

For leg claudication, positive Buerger's test, toe pressure <30 mmHg, or TBI < 0.5, a less urgent referral to a vascular surgeon is recommended.

For asymptomatic peripheral vascular disease, regular vascular assessment should include measurement of the toe pressure and Toe-Brachial Index (TBI) in addition to the Ankle-Brachial Index (ABI). Management comprises of reduction of cardiovascular risk factors, and secondary prevention measures, which may be by a physician.

b) An urgent review by an orthopaedic surgeon is recommended when there is an acute Charcot foot, which often presents with pain, erythema, warmth and swelling in a neuropathic foot with intact skin, and which progresses to multiple joint dislocations, pathological fractures and debilitating foot and ankle deformities.

Table 17 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, or if there is redness or pus, **Do** consult your doctor and 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 elbow first to ensure not too hot. ✓ **Do** pat dry especially in between toes. ✓ **Do** use moisturizing cream on the top of the feet every day, avoiding the areas in between the toes. **Do** use foot balm on dry or cracked soles, but don't walk barefoot after that **Socks / Hosiery** ✓ **Do** wear cotton socks or stockings and ensure they 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 or ingrown toenails yourself. × **Don't** use corn plasters, or acid treatments. **General Hints** × **Don't** smoke. × **Don't** walk barefoot. Always wear footwear inside and outside the house. × **Don't** soak your feet for a long time in very hot or cold water × **Don't** have vigorous massages reflexology or acupuncture on your feet, especially if you have numb or cold feet.

Table 18 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 with socks are acceptable in certain situations. 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 or clogs. × **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 the mother and foetus. In order to reduce the incidence of such complications, good glycaemic control prior to and during pregnancy is important.[297-298]

With an increasing number of older women going on to have children, gestational diabetes mellitus (GDM) has become increasingly important. The prevalence of GDM is approximately 5–10% of all pregnancies depending on the population studied and the diagnostic tests employed.[299] In Singapore, about 8% of all pregnancies are complicated by GDM.[300-301]

11.2 Definitions

Diabetes mellitus in pregnancy falls into 2 categories:

Gestational diabetes mellitus (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.[299,302-304] 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 glucose tolerance in the first trimester are likely to have preexisting diabetes and should be treated in the same manner as women who are diagnosed to have diabetes before pregnancy. In the majority of women with GDM, glucose regulation will return to normal after delivery.[299, 302-303]

Pregestational diabetes is diagnosed when the woman has diabetes before the onset of pregnancy.

11.3 Pre-pregnancy counselling

All women with diabetes who are in the reproductive age group should receive prepregnancy counselling.[204,297,305-306] A meta-analysis has demonstrated a significantly lower prevalence of major congenital anomalies in offspring of women who attended prepregnancy counselling.[307]

Wherever possible, prepregnancy counselling should be performed jointly by a multi-disciplinary team skilled in diabetes care, including the physician, obstetrician, dietician, nurse-educator and other specialists. Its aims are:

- to provide education and counselling about the risk of congenital malformation associated with unplanned pregnancy and poor glycaemic control
- to assess suitability for pregnancy
- to look for complications of diabetes (especially retinopathy and nephropathy) and to evaluate and treat these complications prior to the onset of pregnancy
- to adjust and convert drugs like oral glucose-lowering drugs, some antihypertensive medications, 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 glycaemic 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 supplementation

B All women with diabetes in the reproductive age group should receive prepregnancy counselling, particularly before starting a family.

Grade B, Level 1-

GPP Wherever possible, prepregnancy counselling should be performed jointly by a multi-disciplinary team skilled in diabetes care, including the physician, obstetrician, dietician, nurse-educator and other specialists.

GPP

11.4 Screening for and diagnosis of gestational diabetes

Deterioration of glucose tolerance occurs during pregnancy, particularly in the late second and third trimesters. There is lack of uniformity in the approach to screening and diagnosis of GDM internationally.

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, a large-scale (~25,000 pregnant women) multinational observational study, demonstrated that the risk of adverse maternal, foetal and neonatal outcomes correlated positively with maternal glycaemia at 24–28 weeks of gestation in a continuous linear association.[308] This is true even within glucose ranges previously considered normal in pregnancy. There is no threshold for risk in most of the complications. A revised diagnostic criteria for GDM was recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG).[8] The new diagnostic cut points for the fasting, 1-h and 2-h plasma glucose measurements were developed based on the glucose levels that conveyed an odds ratio for adverse outcomes of at least 1.75 compared with the mean glucose levels in the HAPO study.

Although some countries have adopted the revised diagnostic criteria, the benefits of using the revised diagnostic criteria are uncertain at this time and further studies and analysis will be required before implementing it locally.

Screening

D Risk assessment for gestational diabetes should be undertaken at the first antenatal visit.[105]

Grade D, Level 4

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

- body mass index (BMI) of >25.0 kg/m^2
- first-degree relatives with diabetes
- 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 a 75 g oral glucose tolerance test (OGTT) as early in pregnancy as feasible.[299,302-303] Re-evaluation should be performed at 24–28 weeks of gestation if glucose intolerance is not present at the early screen.

B Women at high-risk for gestational diabetes (GDM) should undergo an oral glucose tolerance test as early in pregnancy as feasible. Re-evaluation should be performed at 24–28 weeks of gestation if glucose intolerance is not present at the early screen.

Grade B, Level 1+

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
- no family history of diabetes

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.[309]

D In pregnant women who are not at high risk for gestational diabetes, 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 D, Level 3

Diagnosis

B Gestational diabetes is diagnosed with a 75 g oral glucose tolerance test (OGTT). A fasting venous plasma glucose ≥7.0 mmol/l or a 2-hour venous plasma glucose of ≥7.8 mmol/l is diagnostic of gestational diabetes.[310] Casual venous plasma levels ≥11.1 mmol/l on 2 successive occasions would confirm gestational diabetes without recourse to oral glucose tolerance testing.

Grade B, Level 1

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

Close surveillance of the mother and foetus must be maintained in all instances of diabetes in pregnancy. All women with pregestational diabetes or diagnosed with gestational diabetes should receive specialised care.[311]

D All women diagnosed with pregestational diabetes or gestational diabetes should receive specialised care.

Grade D, Level 3

Glycaemic management

In gestational diabetes, dietary control should be used in the first instance to attain glycaemic goals without excessive ketonaemia and ketonuria.[303,311-312] Sweet foods should be avoided and caloric intake reduced if the woman is overweight or obese. The diet should contain more complex carbohydrates, more fibre and less saturated fat. Nutritional counselling should be individualised to take into account the patient's body weight, 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 1-hour postprandial capillary glucose of <7.8 mmol/l 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.[299] This is particularly in association with evidence of a macrosomic foetus.

B In gestational diabetes, dietary control should be used in the first instance to attain glycaemic goals. Sweet foods should be avoided and caloric intake reduced if the woman is overweight or obese. The diet should contain more complex carbohydrates, more fibre, and less saturated fat. Nutritional counselling should be individualised, taking into account the patient's body weight, weight gain and physical activity.

Grade B, Level 2++

B If nutritional therapy does not consistently maintain a fasting or pre-meal capillary blood glucose of <5.5 mmol/l and/or a 1-hour postprandial capillary glucose of <7.8 mmol/l 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 2++

Neutral protamine Hagedorn (NPH) insulin remains the basal insulin of choice in pregnancy.[299,305,311-312] Recent data has shown the non-inferiority of insulin detemir, a basal insulin analogue, in pregnant women with type 1 diabetes.[313] Emerging data on the safety and efficacy of insulin analogues will be particularly pertinent to women with pregestational diabetes, in both the type 1 and type 2 diabetes populations. Rapid-acting insulin analogues, aspart and lispro, have been investigated in pregnancy, demonstrating clinical efficacy, minimal transplacental transfer, and no evidence of teratogenesis.[314-317] Insulin aspart and lispro may produce better postprandial control with less hypoglycaemia compared with the use of premeal regular insulin.[314-317] Insulin aspart or lispro should be considered if the woman develops frequent delayed postprandial hypoglycaemia while using regular insulin.

Insulin therapy should be individualised to achieve the glycaemic goals stated previously. Sometimes a multi-dose regimen of insulin administration is needed. In women with pregestational diabetes,

intensive (multi-dose) insulin therapy is often necessary to maintain near-normal glucose control.[318]

C In pregestational diabetes, individualised intensive (multi-dose) insulin therapy is often necessary to achieve and maintain target blood glucose levels.

Grade C, Level 2+

The tight control of blood glucose 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.[319] The management strategy should be to maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting state or pre-meals, and/or <7.8 mmol/l at 1 hour, or <6.7 mmol/l at 2 hours postprandial.[299, 311]

D Maintain maternal capillary blood glucose concentrations as near normal as possible at <5.5 mmol/l in the fasting or pre-meal state, and/or <7.8 mmol/l one hour after meals, or <6.7 mmol/l two hours after meals.

Grade D, Level 4

D Self-monitoring of blood glucose (SMBG) is essential during pregnancy for women gestational diabetes and pregestational diabetes. Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycaemic targets.[320-321]

Grade D, Level 3

D Women with pregestational type 1 diabetes should be advised to test for ketonuria or ketonaemia if they become hyperglycaemic or unwell.[312]

Grade D, Level 4

Multiple studies have been published regarding the use of oral glucose-lowering drugs in pregnancy. Metformin and glibenclamide have been shown to be as effective as insulin for the treatment of GDM[322-324] but long-term safety has not been established. There has been extensive clinical experience with the use of metformin in pregnancy over more

than a quarter of a century. Metformin crosses the placenta freely, but there appear to have been no teratogenic problems. However, the safety of metformin use in early pregnancy has not been systematically examined. The Metformin in Gestational Diabetes (MiG) study demonstrated that metformin can be a viable alternative to insulin in a proportion of women with GDM. Some countries have included metformin as an option for treatment of GDM.

Although both metformin and glibenclamide appear safe for the treatment of pregestational type 2 diabetes, more studies are needed to identify risks and benefits of oral glucose-lowering drugs for the treatment of pregestational diabetes. Women with pregestational type 2 diabetes who become pregnant while taking oral glucose-lowering drugs should be switched to insulin therapy.[303,305] Oral glucose-lowering drugs are currently not recommended during pregnancy[299,302,305] under normal circumstances.

D Oral glucose-lowering drugs are not recommended during pregnancy under normal circumstances. Women with pregestational type 2 diabetes who become pregnant while taking oral glucose-lowering drugs should be switched to insulin therapy.

Grade D, Level 4

Foetal surveillance

D An early pregnancy scan should be performed to confirm viability and accurately date the pregnancy in women with pregestational diabetes, especially when glycaemic control is suboptimal or changes in medications are required.[312]

Grade D, Level 4

B A detailed foetal anomaly scan, including four-chamber cardiac view and outflow tracts, should be performed between 18–22 weeks in women with pregestational diabetes or when overt diabetes is diagnosed in the early pregnancy.[303,306,312]

Grade B, Level 2+

In pregnancies complicated by diabetes, the foetus is at risk of both macrosomia and intrauterine growth retardation (IUGR). The risk of macrosomia is greater when there has been poor glycaemic control.

The risk of IUGR is greater in women with vascular complications of diabetes (retinopathy, nephropathy) or when pre-eclampsia develops.

D Women with pregestational diabetes and gestational diabetes should be offered ultrasound monitoring of foetal growth (foetal abdominal circumference and/or estimated foetal weight) and amniotic fluid volume every 4 weeks from 28 to 36 weeks.[312]

Grade D, Level 4

D Mothers with gestational diabetes and pregestational diabetes should be taught to monitor foetal movements during the last 10–12 weeks of pregnancy and to report immediately any reduction in the perception of foetal movements.[299, 325]

Grade D, Level 4

C 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.[326]

Grade C, Level 2+

Maternal surveillance

C In women with gestational diabetes as well as those with pregestational diabetes, the measurement of blood pressure and dipstick testing for urinary protein is recommended at each antenatal visit to detect the development of pregnancy-induced hypertension and pre-eclampsia, especially if there is pre-existing nephropathy.[299,311]

Grade C, Level 2+

GPP Women with pregestational diabetes should have their serum creatinine and electrolytes assessed at the first antenatal visit and in the third trimester.

GPP

B For women with pregestational diabetes, a retinal assessment should be performed as soon as possible after the first antenatal visit if it has not been done in the preceding 12 months.[312] If any diabetic retinopathy is present, an additional assessment should be performed at 16–20 weeks of gestation. If the first assessment is normal, an assessment should be repeated at 28 weeks of gestation.

Grade B, Level 2++

GPP More frequent assessment may be required in women with poor glycaemic control, hypertension and/or pre-existing retinopathy.[311]

GPP

Preterm labour in women with diabetes

Pregestational diabetes or gestational diabetes are not considered a contraindication to antenatal corticosteroids for foetal lung maturation or to tocolysis.[299]

D Women with insulin-treated pregestational diabetes or gestational diabetes who are receiving corticosteroids for foetal lung maturation should receive additional insulin treatment and close monitoring of glucose levels.[303, 312]

Grade D, Level 4

B Betamimetic drugs (e.g., salbutamol) should not be used for tocolysis in women with diabetes as they may lead to significant hyperglycaemia.[303, 312]

Grade B, Level 2++

Timing and route of delivery

There is no clear evidence regarding the optimal timing for delivery in women with pregestational diabetes and gestational diabetes.

D Delivery should be at term for women with pregestational diabetes and GDM unless specific obstetric or medical factors dictate otherwise (e.g., foetal macrosomia, poor glycaemic control, polyhydramnios, pre-eclampsia, intrauterine growth restriction).[303]

Grade D, Level 4

D Vaginal delivery is preferable unless there is an obstetric or medical contraindication. The presence of diabetes should not itself constitute an indication for elective caesarean delivery.[312]

Grade D, Level 4

Intrapartum management

D During labour and birth, capillary blood glucose should be monitored every 1–4 hours in women with pregestational diabetes and GDM and maintained at 4–7 mmol/l.[303, 311-312]

Grade D, Level 4

D Intravenous dextrose and insulin infusion is recommended during labour and birth for women whose blood glucose is not maintained at 4–7 mmol/l.[311-312]

Grade D, Level 4

D Women with pregestational type 1 diabetes should be considered for intravenous dextrose and insulin infusion from the onset of established labour.[312]

Grade D, Level 4

11.6 Management of the infant of a woman with diabetes

D The neonatologist should be informed of deliveries of infants of women with diabetes so that possible complications like neonatal hypoglycaemia may be monitored and treated early.

Grade D, Level 4

C Screening for abnormalities should also be performed in infants of woman with diabetes soon after birth.[303]

Grade C, Level 2+

D Babies of women with diabetes should be fed as soon as possible after birth (within 30 minutes).[312]

Grade D, Level 4

D Infants of women with diabetes who present with clinical signs of hypoglycaemia should have their blood glucose tested and be treated with intravenous dextrose as soon as possible.[312] Close monitoring

of blood glucose levels is necessary within the first 48 hours of the baby's life.

Grade D, Level 4

D 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. [312]

Grade D, Level 4

11.7 Postnatal management

Glycaemic management

The majority of women with gestational diabetes return to normal glucose tolerance immediately after delivery.[299]

D Women with gestational diabetes should discontinue glucose-lowering treatment immediately after birth and monitor their blood glucose levels. [311]

Grade D, Level 4

D Women with insulin-treated pregestational diabetes should reduce their insulin doses immediately after birth and monitor their blood glucose levels carefully to establish the appropriate dose.[303, 312]

Grade D, Level 4

GPP Women who are treated with insulin post-delivery should be informed that they are at increased risk of hypoglycaemia in the postnatal period, especially when breastfeeding, and should be advised to have a meal or snack available before or during feeds.

GPP

Breastfeeding

D Breastfeeding is recommended for infants of women with diabetes.[327-329]

Grade D, Level 3

GPP Insulin is recommended for glycaemic control in women with diabetes who breastfeed.

GPP

Although some small studies have shown that metformin may be safe for the infants in women who breastfeed,[327-329] there is still insufficient evidence to recommend the use of oral glucose-lowering agents in women who breastfeed.

GPP Women with pregestational diabetes who are breastfeeding should continue to avoid any drugs for the treatment of diabetes complications that were discontinued for safety reasons in the pre-conception period.

GPP

Postnatal glucose tolerance testing for women with gestational diabetes

B All subsequent pregnancies in women with gestational diabetes carry a risk for gestational diabetes. Early evaluation of glucose tolerance in future pregnancies should be stressed.[105, 330]

Grade B, Level 2++

Women with GDM are at increased risk for developing diabetes subsequently[105, 330] and some cases of GDM may represent pre-existing undiagnosed type 2 diabetes.[105] Therefore, a 75 g 2-h OGTT should be performed 6–12 weeks postpartum and the patient reclassified according to criteria accepted in the non-pregnant state.[105,299,302,311]

D Women with a history of gestational diabetes should be offered lifestyle advice aimed at diet modification, weight control and increasing physical activity to reduce their risk of subsequent development of diabetes.[299, 302, 312]

Grade D, Level 4

For women with a history of GDM, all subsequent pregnancies carry a risk for the development of GDM. Such women should have lifelong screening for the development of prediabetes or diabetes at least once every 3 years.[105]

C For women with gestational diabetes, a 75 g 2-h oral glucose tolerance test (OGTT) should be performed 6–12 weeks postpartum

and the woman reclassified and counselled according to criteria accepted in the non-pregnant state.[105]

Grade C, Level 2+

D Women with a history of gestational diabetes should have lifelong screening for the development of prediabetes or diabetes at least once every 3 years.[311]

Grade D, Level 4

11.8 Contraception

D In women with prediabetes or overt diabetes, 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/or other risk factors for vascular disease.[311,331] Progestin-only preparations may be suitable for these women.[311]

Grade D, Level 3

There is concern about the risk of infection with intrauterine device (IUD) use. Women with diabetes are particularly susceptible to bacterial infection.

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

D Low-dose oestrogen-progestin oral contraceptives and intrauterine devices (IUD) are not contraindicated in women with previous gestational diabetes.[332]

Grade D, Level 3

D Oestrogen-progestogen contraceptives should be avoided in women with complications of diabetes and/or other risk factors for vascular disease.[311]

Grade D, Level 3

12 Management of the child and adolescent with diabetes mellitus

12.1 Introduction

Type 1 diabetes mellitus is the predominant form of diabetes affecting children in Singapore despite the emergence of type 2 diabetes.

The incidence of childhood type 1 diabetes in Singapore is relatively low compared with developed countries at 2.46 per 100,000 children aged 1-12 years.[333] Yet, it remains the predominant form of diabetes affecting children in Singapore. Although corresponding local incidence data is unavailable, type 2 diabetes in children and adolescents is an increasingly important public health concern both in Asia[334-335] and worldwide.[336] Unlike type 1 diabetes, type 2 diabetes is often associated with risk factors for cardiovascular disease that may already be present at the time of diagnosis.[26, 337-338]

Early diagnosis and treatment of type 1 diabetes is mandatory

Health professionals managing diabetes mellitus in children and adolescents must recognise differences between the treatment challenges of these two disorders.[336] Early recognition and diagnosis of type 1 diabetes mellitus is mandatory and may be life-saving. However, it may be difficult to distinguish between the two types of diabetes, especially in overweight children. Therefore, we recommend that children and adolescents with suspected diabetes be referred to a specialist promptly for early assessment, where possible, on the same day.

GPP Children and adolescents with suspected diabetes should be referred to a specialist for early assessment, where possible, on the same day.

GPP

12.2 Management principles

Provide age-appropriate diabetes education and care

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,[339-340] with a program of ongoing and structured diabetes education. Diabetes education remains the foundation of good diabetes control.[341] This includes ensuring that parent and child learn about blood glucose monitoring, insulin administration as well as hypoglycaemia and sick day management.[342]

B Children and adolescents with either type 1 diabetes or type 2 diabetes should be provided ongoing and structured diabetes care by a multi-disciplinary diabetes care team.

Grade B, Level 2^{++}

As the child matures, age-appropriate diabetes education should be imparted, emphasizing on self-care responsibilities shifting from parent to patient, under parental guidance and supervision.[343-344] This balance between adult supervision and self-care should be defined and evolve according to the individual's physical, psychological and emotional maturity.

GPP Diabetes education should involve the family and child to include learning about blood glucose monitoring, insulin administration, hypoglycaemia and sick day management. As the child matures, diabetes education should emphasise self-care responsibilities shifting from the parent to child, under parental guidance and supervision.

GPP

Adolescence is characterised by distractions and changing demands;[345-346] blood glucose (BG) control is poorer[347] and clinic attrition rates are high.[348] However, optimal care for adolescents with diabetes has not been subjected to rigorous scientific studies. Care during adolescence should focus on psycho-educational interventions, as the beneficial effects on psychological outcomes are greater than on glycaemic control.[349] Care that focuses on the planned transition of youth from paediatric to adult diabetes health care is strongly encouraged.[350-351]

D Include psycho-educational intervention strategies and planned transition in the management of adolescents with diabetes.

Grade D, Level 4

12.3 Treatment goals

The treatment goals for children and adolescents with type 1 diabetes mellitus and type 2 diabetes mellitus are distinct.

The goals of treatment for childhood and adolescent type 1 diabetes mellitus include [340,352]:

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

The goals of treatment for childhood and adolescent type 2 diabetes mellitus include [4]:

a. Weight loss
b. Increase in exercise capacity
c. Normalization of blood glucose
d. Control of co-morbidities

12.4 Targets of glycaemic control

The goal is to obtain the lowest possible HbA_{1c} without hypoglycaemia[336]

Targets must be given with the expectation that careful attention will be taken to avoid severe hypoglycaemia. Targets must be increased in children and adolescents with hypoglycaemia unawareness.[353] As a guideline, the optimal fasting/pre-prandial blood glucose is 5.0-8.0mmol/l, the optimal post-prandial blood glucose level ranges from 5.0-10.0mmol/l and the ideal nocturnal blood glucose level ranges from 4.5-9.0mmol/l.[353]

GPP Blood glucose targets should be individually determined with a goal to achieving a value as close to normal as possible as there is little age-related scientific evidence for strict glucose targets.

GPP

A Children and adolescents with type 1 diabetes mellitus or type 2 diabetes mellitus, and their families should be informed that the target for long term blood glucose control is a HbA_{1c} level of less than 7.5% or 58.5 mmol/mol without frequent hypoglycaemia.

Grade A, Level 1+

Self-monitoring of blood glucose is an essential tool in the optimal management of childhood and adolescent diabetes[353]

Self-monitoring of blood glucose helps to monitor immediate and daily levels of control, determine immediate and daily insulin requirements and helps guide insulin adjustments to decrease fluctuations in BG levels.[353] It also detects hypoglycaemia and assists in its management, as well as allows the safe management of hyperglycemia.[353]

A Children and adolescents with type 1 diabetes should be encouraged to use blood glucose measurements for monitoring of glycaemic control because it is associated with reduced levels of HbA_{1c}.

Grade A, Level 1+

GPP Consider the possibility of antecedent nocturnal hypoglycaemia if fasting blood glucose is <4mmol/l.

GPP

12.5 Diagnosis

The diagnostic criteria for paediatric diabetes is similar to adult criteria, however definitions for IFG and IGT differ.

For children, the glucose challenge as performed and described by the WHO uses a glucose load of 1.75g glucose per kg body weight (maximum 75g).

It is important to distinguish type 2 diabetes from type 1 diabetes.

The clinician must weigh the evidence in each child or adolescent to distinguish between type 1 diabetes and type 2 diabetes, noting that:

a. As many as 15-25% of newly diagnosed type 1 diabetes children and adolescents may be obese[336] and
b. A significant number of paediatric type 2 diabetes patients may present with ketonuria or ketoacidosis at diagnosis.

Targeted screening for type 2 diabetes in children and adolescents

C Screening for type 2 diabetes in asymptomatic children and adolescents is *not recommended* as a public health strategy.[354]

Grade C, Level 2+

12.6 Treatment of children and adolescents with type 1 diabetes mellitus

GPP Type 1 diabetes mellitus in children and adolescents should be managed by an endocrinologist or physician with a special interest in childhood diabetes.

GPP

Children and adolescents with type 1 diabetes mellitus are dependent on insulin for survival. Many formulations of insulin are available and most have some role in the management of type 1 diabetes mellitus.

a. Rapid acting insulin analogues
   In pre-pubertal children, the rapid acting insulin analogues (aspart, glulisine, lispro), administered as pre-prandial bolus injections closer to mealtime than regular insulin, can significantly lower post-prandial glucose levels compared with regular insulin.[355-356] 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.[357-358]

b. Basal insulin analogues
   The basal insulin analogues, glargine and detemir, show a more predictable insulin effect with less day to day variation,

compared to NPH insulin.[359-360] Glargine has the advantage of once-daily administration, with the potential of reducing the risk of nocturnal hypoglycaemia. Once daily insulin glargine allows a comparable or small improvement in HbA_{1c} and greater treatment satisfaction in adolescents compared to conventional basal insulins.[361] In adults, studies with detemir have shown weight reduction or less weight gain,[362] which has been observed also in children and adolescents.[360]

The choice of insulin regimen will depend on many factors including: age, duration of diabetes, lifestyle, targets of metabolic control and particularly patient/family preferences.

a. The aim is to achieve as close to physiological insulin replacement as possible and optimal glycaemic control, which should include the consideration of an intensive insulin regimen.
b. There are presently no safety concerns that would preclude the use of insulin analogues in the paediatric age group.[363]

C Self-monitoring of blood glucose is an essential tool in the optimal management of childhood and adolescent type 1 diabetes mellitus and should be used in conjunction with insulin treatment.[353]

Grade C, Level 2+

a. The frequency of self-monitoring of blood glucose correlates with improved glycaemic control.[364]
b. Without accurate monitoring, the risks of acute crises and long term vascular and other damaging complications are greatly increased, leading to high levels of healthcare costs and personal disability.[353]

Annual screening is important to diagnose coincident autoimmune illness and complications of type 1 diabetes mellitus.

C Children and adolescents with type 1 diabetes mellitus should be offered screening for:

- Thyroid disease at diagnosis and annually thereafter.
- Retinopathy annually from the age of 12 years.
- Microalbuminuria annually from the age of 12 years.

Grade C, Level 2+

12.7 Treatment of children and adolescents with type 2 diabetes mellitus

Recognise the heterogenic manifestations of type 2 diabetes mellitus in children.

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. Consider early consultation and referral to the endocrinologist especially with acute emergencies.[365]

a. Pre-adolescent children are unlikely to have type 2 diabetes mellitus, even if obese.[366]
b. Overweight diabetic adolescents should have both type 1 and type 2 diabetes considered as differentials.[366-367] Antibody determination is the only way to definitively determine the presence of autoimmune diabetes (type 1 diabetes).

Lifestyle modification is the cornerstone of type 2 diabetes mellitus management in children.

The less ill child with type 2 diabetes mellitus 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.[365] With time, metabolic control may change, necessitating the re-evaluation of treatment, such as tapering of insulin and the introduction of an oral agent.

a. Lifestyle changes in diet and exercise are essential and should be recommended for all children with type 2 diabetes[336] and continued even after addition of pharmacologic therapy.
b. Initial treatment modality is determined by symptoms, severity of hyperglycemia, and presence or absence of ketoacidosis. As in type 1 diabetes mellitus, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and appropriate treatment.

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

Grade C, Level 2+

C Lifestyle changes in diet and exercise should be recommended for all children with type 2 diabetes mellitus and continued, even after addition of pharmacologic therapy.

Grade C, Level 2+

Insulin and Metformin can be considered for the treatment of type 2 diabetes mellitus in children.

Metformin is recommended as the first-line oral agent in children and adolescents with type 2 diabetes mellitus.

a. It does not predispose to hypoglycaemia, body weight often remains stable with metformin, and it is relatively safe and effective.[365,368]
b. 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.
c. Metformin may normalise ovulatory abnormalities in girls with polycystic ovarian syndrome and increase pregnancy risk.

C Metformin may be started as the first-line oral agent in children with type 2 diabetes mellitus if blood glucose targets are not achieved. Insulin therapy should be started if oral agents fail to attain target control.

Grade C, Level 2+

A 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.

Grade A, Level 1+

A If monotherapy with metformin over 3-6 months has failed, insulin should be added to the treatment.

Grade A, Level 1+

Failure of monotherapy with metformin over 3-6 months indicates a need to add insulin. Insulin sensitisers (thiazolidinediones) and secretagogues (meglitinide/repanglinide), glucosidase inhibitors (acarbose), incretin mimetics (GLP-1 receptor agonists) and DPP-IV inhibitors have yet to be approved for use in children and adolescents under 18 years old.[336]

The aggregation of risk factors for cardiovascular disease in the presence of insulin resistance and diabetes may result in higher risk for coronary events and increased mortality in young adulthood.

C Children and adolescents with type 2 diabetes mellitus should be offered co-morbidity screening for:

- Albuminuria at diagnosis and annually thereafter.
- Hypertension at diagnosis and annually thereafter.
- Dyslipidaemia soon after diagnosis and annually thereafter.

Grade C, Level 2+

Co-morbidities are commonly seen early in the course of type 2 diabetes mellitus and should be tested for sooner than type 1 diabetes mellitus.

Either micro- or macro-albuminuria and/or hypertension may be present at the time of diagnosis.[338]

GPP Albuminuria should be evaluated at diagnosis and blood pressure should be evaluated at every visit. Confirmed hypertension (BP>95% for age, gender and height) or albuminuria can be treated with an angiotensin-converting enzyme (ACE) inhibitor.

GPP

Testing for dyslipidaemia should be performed soon after and annually thereafter.[337-338]

GPP Pharmacotherapy is warranted if low density lipoprotein remains elevated (≥3.4mmol/l) after 6 months of optimised glucose control and diet.[369] Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention,[369] although long term safety data are not available.

GPP

GPP Evaluation for non-alcoholic fatty liver disease (NAFLD) and inquiries about puberty, menstrual irregularities and obstructive sleep apnea should be done at diagnosis and annually thereafter.

GPP

13 Diagnosis and management of the adult with type 1 diabetes mellitus

13.1 Introduction

Type 1 diabetes accounts for 5-10% of all with diabetes and is a result of the destruction of the β-cells of the pancreas.[370] Although more commonly presenting in children and adolescents, type 1 diabetes may present at any age. The rate of β-cell destruction may be very variable: it may be rapid in some (leading to ketoacidosis as the first manifestation of the disease) to retention of residual β-cell function sufficient to prevent ketoacidosis for many years.[370] All these individuals are dependent on insulin for survival and are at risk for ketoacidosis, hence requiring immediate medical treatment with concomitant education.

13.2 Diagnosis

GPP Patients who are suspected to have type 1 diabetes should be referred to the specialist promptly for assessment.

GPP

Markers of immune destruction of the β-cell like autoantibodies to Glutamic Acid Decarboxylase (GAD may be present in 85-90% of individuals when fasting hyperglycaemia is initially detected. However, β-cell autoantibodies are present in just 40% of the Singaporean/Asian type 1 diabetes population.[371-372] The absence of GAD antibodies should therefore not preclude a diagnosis of type 1 diabetes.

A high index of suspicion is required to diagnose type 1 diabetes. Those who are lean and hyperglycaemic despite multiple oral glucose lowering agents, or those who experience an abrupt deterioration in their glycaemic control ought to be evaluated further with a GAD antibody, and random glucose and C-peptide to assess their endogenous insulin reserve.[370] They should also be referred to a specialist for further assessment. Uncertainty about the absolute need for insulin should prompt a referral to a specialist for further assessment.

13.3 Insulin treatment

GPP Individuals with type 1 diabetes should have access to a multidisciplinary team consisting of an endocrinologist, a nurse educator, a dietitian and a mental health professional qualified to provide up to date education and support.

GPP

A Most people with type 1 diabetes should be treated with multiple dose insulin (MDI) injections (at least three injections per day of prandial insulin and at least one injection per day of basal insulin) or continuous subcutaneous insulin infusion (CSII).[18, 25]

Grade A, Level 1+

The Diabetes Control and Complications trial (DCCT) was a randomised controlled trial comparing standard therapy to more intensive therapy, while the Epidemiology of Diabetes Interventions and Complications (EDIC) study described the outcomes of the DCCT cohort ten years later. Both these studies clearly showed that intensive insulin therapy (three or more insulin injections) was a key part in improving glycaemia and resulted in better microvascular[25] and macrovascular outcomes.[18]

A Most people with type 1 diabetes should use insulin analogues to reduce the risk of hypoglycaemia.[373-374]

Grade A, Level 1+

Short- and intermediate-acting human insulins were used in the DCCT. There was a high rate of severe hypoglycaemia with intensive insulin therapy. Rapid-acting and long-acting insulin analogues have since been shown to be associated with less hypoglycaemia with equivalent HbA_{1c} lowering efficacy in Type 1 diabetes,[373-374] and should be considered.

13.4 Medical nutrition therapy

A Individuals using rapid-acting insulin by injection or insulin pump should adjust the meal and snack insulin doses based on the carbohydrate content of the meals and snacks.[60, 62]

Grade A, Level 1+

The total carbohydrate content of meals and snacks is the primary determinant of bolus insulin doses.[62] There are several methods for determining nutrient content of meals, including experience-based estimation, the exchange system and carbohydrate counting. The DAFNE (Dose Adjustment For Normal Eating) study demonstrated that structured education in advanced carbohydrate counting and using glucose and the insulin to carbohydrate ratio measurements to adjust insulin doses according to carbohydrate intake resulted in improvements in glycaemic control without an increase in severe hypoglycaemia.[60] Despite increases in the number of insulin injections and blood glucose tests, there were positive effects on quality of life, satisfaction with treatment and psychological well-being.

Those who use fixed daily insulin doses, carbohydrate intake should be kept consistent with respect to time and amount.[56,375]

13.5 Structured education and self-management

B People with diabetes should receive diabetes self-management education and ongoing support.[60, 119]

Grade B, Level 2+

People with diabetes undertake most care themselves, away from health settings. Effective diabetes self-management is essential to reduce mortality, diabetes-related complications and quality of life.[119] The DAFNE randomised controlled trial transformed type 1 diabetes self-management demonstrating improvements in glycaemic control, treatment satisfaction, incidence of acute complications and quality of life.[60] There are variations in structured education between courses, but core components[376] usually include:

1. Carbohydrate counting and insulin dose adjustment
2. Hypoglycaemia management
3. Group work
4. Goal setting
5. Empowerment, control and confidence

13.6 Adjustment and psychiatric disorders

C Screening of psychosocial functioning, especially anxiety and depression should be performed.[377-378] Those with positive screening should be referred promptly for treatment.[379]

Grade C, Level 2+

Diabetes is a risk factor for psychiatric disorders like depression[380] and anxiety disorder.[377-378] Those who have recurrent diabetes ketoacidosis are more likely to have depression and anxiety than those without recurrent hospitalisations.[379] As psychiatric illness is often associated with poor metabolic control,[381-382] regular screening for these disorders with diabetes is warranted. Importantly, these disorders tend to persist;[383] those who are found to have these disorders ought to be referred promptly for treatment.

13.7 Associated autoimmune disorders

GPP Patients with type 1 diabetes should have thyroid function checked every 1-2 years.

GPP

The prevalence of autoimmune thyroid disorders in association with type 1 diabetes is as high as 17% and is the most common autoimmune disorder associated with type 1 diabetes.[384] Thyroid function should be monitored every 1-2 years.

14 Prevention of type 2 diabetes mellitus

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.

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.

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.[385-390]

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.

14.1 Who are potential candidates for screening and intervention?

Screening for asymptomatic individuals for type 2 diabetes mellitus should be carried out on an opportunistic basis. Testing should be considered in adults of any age who have one or more risk factors for diabetes. In those without risk factors, testing should begin at 40 years.[391]

The risk factors for diabetes are:

- Overweight/obesity (body mass index 25.0 kg/m^2 or greater)
- First degree relative with diabetes
- High risk race/ethnicity
- Women who delivered a baby 4kg or more; or were diagnosed with Gestational Diabetes Mellitus
- Hypertension (>140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level <1.0mmol/L (male), <1.3mmol/L (female) and/or a triglyceride level >2.2mmol/L
- Women with Polycystic ovary disease
- Impaired fasting glycemia (IFG) or impaired glucose tolerance (IGT) on previous testing
- History of cardiovascular disease

Current consensus information suggests that individuals who are at increased risk of developing diabetes may be identified by the definitions of IFG and IGT.

B Screening for asymptomatic individuals for type 2 diabetes mellitus should be carried out on an opportunistic basis. Testing should be considered in adults of any age who have one or more risk factors for diabetes. In those without risk factors, testing should begin at 40 years.

Grade B, Level 2^{++}

14.2 How should diabetes prevention be effected?

It is recommended that patients with IFG or IGT can be given interventions that significantly decrease the rate of onset of diabetes. These interventions include intensive individualised lifestyle

modifications programs; this has been shown to have sustained reduction in the rate of conversion to type 2 diabetes.

In 2 landmark randomised controlled trials, subjects with IGT were randomised to intervention arms which included intensive lifestyle modification. Intensive lifestyle modification has been shown to be very effective.[386-387]

After 6 years in the Da Qing trial, diet, exercise and diet-plus-exercise interventions were associated with 31%, 46% and 42% reductions in risk of developing diabetes.

In the Finnish trial, the risk of developing diabetes was reduced by 58% in the intervention group (individualised counselling, physical activity) after 3.2 years.

In the Diabetes Prevention Program (DPP), the subjects were randomised to one of three intervention groups with an average follow up of 2.8 years.

The lifestyle intervention reduced the incidence by 58% and metformin by 31%, as compared with placebo.

Follow up of these large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes, with 43% reduction at 20 years in the DaQing study, 43% reduction at 7 years in the Finnish Diabetes Prevention study and 34% at 10 years in the US Diabetes Prevention Program Outcomes study.[388-390]

The lifestyle interventions have also been found to be cost effective.[392-393]

Based on the results of these clinical trials, lifestyle changes with modest weight loss (5-10% of body weight) and moderate intensity physical activity (~30 minutes daily) is the treatment of choice with individuals with IFG/ IGT.

A Lifestyle changes with modest weight loss (5-10% of body weight) and moderate intensity physical activity (~30 minutes daily) is the treatment of choice with individuals with impaired fasting glucose / impaired glucose tolerance.

Grade A, Level 1++

The more difficult issue is the role of drug therapy in diabetes prevention. The issue of cost, side effects and persistence / lack of persistence of effect are to be considered.

The results of the DPP trial showed that lifestyle modification was nearly twice as effective in preventing diabetes compared to metformin; that metformin had greater efficacy in preventing diabetes in the younger, very obese individuals. In the DPPOS, the incidence of diabetes 10 years after the DPP randomization was reduced by 18% in the metformin group compared with placebo.[390]

In the STOP-NIDDM trial, the subjects with IGT were randomised, 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%.[394-395] However there has been no follow-up study for the STOP NIDDM trial.

In the XENDOS study, orlistat was examined for its ability to delay type 2 diabetes when added to lifestyle change in subjects with BMI >30 kg/m2 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.[396]

However, this study was not designed as a prevention trial; therefore the effect of the drug in diabetes prevention is not as clearly established as with the other drugs.

In summary, 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. Modest weight loss (5-10% of body weight) and moderate intensity physical activity (~30min daily).

It is recommended that metformin may be considered for the very high risk individual with IFG/ IGT of age < 60, BMI ≥ 35kg/m^2.[50,385,390, 397]

B Metformin may be considered for the very high risk individual (please refer to chapter on Diagnosis and screening) with impaired fasting glucose / impaired glucose tolerance of age < 60 and BMI ≥ 35kg/m^2.

Grade B, Level 2^{++}

15 Clinical quality improvement

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, randomised 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 recognised 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.

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.[148, 398]

* *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.*

† *Accreditation is a formalised procedure by which an organization, discipline or individual is deemed to have met an agreed standard*

15.2 Measurement of quality indicators

The workgroup proposes 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

Process 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
Outcome Quality Indicators **	
HbA_{1c}	Percentage of patients with most recent HbA_{1c} level >9% (poor control)
LDL cholesterol	Percentage of patients with most recent LDL cholesterol <130mg/dl
Blood pressure	Percentage of patients with most recent blood pressure <140/80mmHg

* includes a baseline assessment.
** Antonio Nicolucci, Sheldon Greenfield, Soeren Mattke. Selecting indicators for the quality of diabetes care at the health systems level in OCED countries. International Journal for Quality In Health Care. Sep 2006; 26-30.

A sample of a patient care card is shown in Table 19 (pg 167) to assist both the patient and his/her health care provider in the tracking of these indicators.

Monitoring and implementing diabetes care quality indicators 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 outcomes.

Grade A, Level 1+

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

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 – on Glibenclamide 5 mg om. BP 120/80, Weight 100 kg, Height 1.7 m,
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 (weight)	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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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self-Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://smj.sma.org.sg/cme/smj/index.html (the link will only be available once the June 2014 issue of the SMJ becomes available). The answers will be published in the SMJ August 2014 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Choose True or False for each statement.

		True	False
1.	With regards to diagnosis of diabetes mellitus		
	A) In patients with hyperglycaemic crisis, diabetes mellitus can be diagnosed without further testing	☐	☐
	B) Diabetes mellitus can be diagnosed if fasting plasma glucose is 6.5 mmol/l	☐	☐
	C) When two different tests are available for the same patient and the results for both tests are above the diagnostic thresholds, the diagnosis of diabetes is confirmed	☐	☐
	D) Fasting plasma glucose measured in an accredited laboratory is the preferred test for the diagnosis of diabetes mellitus	☐	☐
2.	With regards to lifestyle modification		
	A) Medical nutrition therapy in diabetes only addresses glycaemic control	☐	☐
	B) A diet for diabetes should contain a good balance of carbohydrate, protein and fat	☐	☐
	C) If weight reduction is needed, it should be attempted rapidly (1.00 to 2.0 kg/week)	☐	☐
	D) All individuals with type 2 diabetes should undertake at least 100 mins/week of moderate to vigorous aerobic exercise	☐	☐

		True	False
3.	With regards to pharmacotherapy		
	A) All patients with type 1 diabetes need insulin treatment	☐	☐
	B) Biguanides (metformin) decrease hepatic glucose release, enhance peripheral glucose disposal and delay glucose absorption	☐	☐
	C) In patients type 2 diabetes, one does not need to monitor for adverse events such as hypoglycaemia or fluid retention	☐	☐
	D) Metformin is the preferred choice for first-line oral glucose lowering therapy	☐	☐
4.	When assessing glycaemic control		
	A) Self-monitoring of blood glucose should be considered for pregnant patients with pre-existing diabetes	☐	☐
	B) Self-monitoring of blood glucose should be carried out 3 or more times daily for patients with type 1 diabetes	☐	☐
	C) Self-monitoring of urine glucose is recommended for monitoring of glycaemic status	☐	☐
	D) Glycated haemoglobin (HbA_{1c}) should be performed routinely in all patients with diabetes, at initial assessment and then as part of follow-up care	☐	☐
5.	In terms of reducing the risk of additional complications in patients with diabetes		
	A) To reduce the risk or slow the progression of nephropathy, optimised blood pressure control is recommended	☐	☐
	B) The recommended time of first eye examination is within one year after diagnosis of diabetes once patient is aged ten years or older	☐	☐
	C) All individuals with diabetes should receive an annual foot examination to identify high-risk foot conditions	☐	☐
	D) Women with diabetes who are in the reproductive age group should receive prepregnancy counselling	☐	☐

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