CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION

SPECIAL EDITION
in Commemoration of the 18th ASEAN Federation of Endocrine Societies (APES) Congress 2015

MALAYSIAN ENDOCRINE & METABOLIC SOCIETY
MINISTRY OF HEALTH MALAYSIA
ACADEMY OF MEDICINE MALAYSIA
DIABETES MALAYSIA
FAMILY MEDICINE SPECIALISTS ASSOCIATION OF MALAYSIA
STATEMENT OF INTENT

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

REVIEW OF THE GUIDELINE

This guideline was issued in December 2015 and will be reviewed in December 2019 or sooner if new evidence becomes available.

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Electronic version is available on the following websites:
http://www.acadmed.org.my
http://www.diabetes.org.my
http://www.endocrine.my
http://www.mems.org.my
http://www.moh.gov.my
Type 2 Diabetes Mellitus (T2DM) remains a major non-communicable disease in Malaysia. This is obviously due to poor lifestyle and made worse by co-existing medical problems including obesity. One of the main issues in the management is screening of the disease at an early stage in order to prevent complications and treat them early.

Patients with T2DM, their caregivers and the society need to be educated and offered holistic management of T2DM. Health education helps to ensure compliance with the treatment. Notwithstanding, healthcare providers need to be equipped with the best and updated knowledge of T2DM management for effective and safe delivery of care to the patients. Variation in practice should be reduced and cost-effective treatment chosen to improve the management at all levels of health care. All these can be addressed, among others, through the availability and accessibility of local clinical practice guidelines (CPG) addressing issues pertaining to T2DM.

I wish to congratulate the CPG Development Group for their relentless effort on updating the CPG on Management of T2DM. It is hoped that this will be followed by various implementation strategies to increase the utilization of the document. At the end of the day, the aim of our service is to provide appropriate and quality healthcare to the patients and society.

Thank you.

Datuk Dr. Noor Hisham Abdullah
Director General of Health
Ministry of Health, Malaysia
The incidence of diabetes in Malaysia is on a relentless march superseding any previous projections made by IDF and WHO. From 1996 till 2011 the rate of growth in the number of patients with diabetes has stayed high at 80% over a 10-year period. If this rate remains unabated by 2020 when Malaysia attained a developed nation status it is predicted that more than a third of adults above the age of 30 would have developed the disease, matching those seen among urban dwellers in the Middle East. Every effort should be made to slow this progression and what better way than to focus on our children by introducing healthy living as a core curriculum in primary schools. If this and other steps are successful, we will only begin to witness a fall in the incidence of diabetes a generation later or to be precise twenty years from now. In the meantime society and the country as a whole has to bear the immense health and economic burden of the disease.

Another matter that needs our utmost attention is our inability to improve significantly the body politic of our diabetes control. Based on the Diabcare 2008 and 2013 studies involving tertiary centres and the National Diabetes Registry 2009 and 2012 consisting of mainly primary care data, the percentage of patients whose diabetes were under control remained unchanged during those periods; an appalling 13% for tertiary institutions and 24% for primary care. This happened despite the fact that in tertiary institutions, there had been an increase in the utilisation of insulin from 54% in 2008 to 65% in 2013. It boiled down to the failure to ensure compliance, particularly among those who were on insulin. In general, the rate of compliance to insulin was a mere 64%, i.e. more than a third of our patients were not injecting according to instructions.

Diabetes seems to bring out the worst in our patients. It is time that we bring our patients to the negotiation table and to hear straight from the horses’ mouth what they are willing or not willing to take. Likewise, it’s about time patient advocates and health authorities realise the importance of allowing health caregivers to increase their fees for the additional time spent on the medical consultation as a means of enhancing patient’s compliance to therapy. We are not going to make any significant headway in improving patient’s compliance without spending enough time counseling them.

There have been several noteworthy changes to this fifth edition of the CPG. Eleven new chapters had been added, including a first for a CPG of its sort; a section on female sexual dysfunction. Treatment algorithms have multiplied to include those who are on follow-up and those with specific patient profiles. The management of acute diabetic emergencies features prominently with step by step detailed protocols. In essence, the CPG tries to cover as much ground as possible while not compromising on the need for a concise account of diabetes management.

For the first time, the CPG has been revised with the support of neither pharmaceutical companies nor governmental institutions thus ensuring its scientific impartiality. It has been a tremendous team effort involving numerous individuals, in particular, members of the development committee, reviewers and secretarial staff while not forgetting the editorial team that painstakingly reviewed every single reference in the CPG. No amount of words can truly express our gratitude. The experience has been really rewarding and I for one found it to be very educational.

Prof. Dr. Nor Azmi Kamaruddin  
Chairperson  
Clinical Practice Guidelines Development Group
GUIDELINE DEVELOPMENT AND OBJECTIVES

Guideline Development

The guideline development task force consisted of endocrinologists, paediatric endocrinologist, family medicine specialist, public health physician, general physicians and dietitians.

The previous edition of the Clinical Practice Guidelines (CPG) on Management of Type 2 Diabetes Mellitus (T2DM) 2009 was used as the basis for the development of this present guideline.

Literature search was carried out at the following electronic databases: PUBMED, Medline, Cochrane Databases of Systematic Reviews (CDSR), Journal full text via OVID search engine. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies.


This guideline is based largely on the findings of systematic reviews and meta-analyses in the literature, taking into consideration local practices.

The clinical questions were divided into major subgroups and members of the task force were assigned individual topics within these subgroups. The task force met a total of twelve times throughout the development of the guideline. All literature retrieved were critically appraised, presented and discussed during group meetings. All statements and recommendations formulated were agreed by the task force members. Where the evidence was insufficient, the recommendations were derived by consensus of the task force members.

The articles were graded using the criteria used by the United States/Canadian Preventive Services Task Force, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guideline was posted on the Malaysian Endocrine and Metabolic Society (MEMS) and Ministry of Health Malaysia websites for comment and feedback. This guideline had also been presented to the Technical Advisory Committee for Clinical Practice Guidelines and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.
Objectives

The aim of the guideline is to provide evidence-based recommendations to assist healthcare providers in the identification, diagnosis and management of patients with type 2 diabetes mellitus.

Clinical Questions

The main clinical questions of this guideline are:
1. How best to diagnose diabetes and abnormal glucose tolerance?
2. How can patients with diabetes best managed?
3. How to treat the acute complications of diabetes?
4. How best to manage the chronic complications of diabetes?
5. How best to manage diabetes in special populations?
6. How to prevent diabetes?
7. How to address the issue of unproven therapies, traditional and complementary medicine in diabetes?

New Contents

The following are new additions to the CPG:
1. Using A1c as a screening and diagnostic test for type 2 diabetes mellitus
2. Cardiovascular risk estimation
3. Algorithm for patients on follow-up
4. Algorithm for specific patient’s profiles
5. Table of efficacy of various anti-diabetic agents
6. Management of diabetic emergencies (hypoglycaemia, diabetic ketoacidosis and hyperglycaemic hyperosmolar state)
7. Female sexual dysfunction
8. Mental health issues in diabetes
9. Management of diabetes in acute illnesses, stress and surgery
10. Diabetes in special populations (gestational diabetes mellitus, adolescents, elderly, Ramadan)
11. Unproven therapies in type 2 diabetes mellitus

Target Population

This guideline is applicable to all adolescents, adults and pregnant ladies with diabetes as well as those at risk of developing diabetes.

Target Groups

This guideline is meant for all healthcare professionals involved in treating patients with T2DM which includes: medical officers, family medicine specialists, primary care physicians, general practitioners, public health personnel, general physicians, endocrinologists, cardiologists, nephrologists, neurologists, geriatricians, obstetricians and gynaecologists, paediatricians, ophthalmologists, dentists, nurses, assistant medical officers, podiatrists, pharmacists, dietitians as well as diabetic nurse educators.
THE MAIN CLINICAL INDICATOR FOR QUALITY MANAGEMENT

• Proportion of patients with diabetes with A1c ≤6.5%
• Numerator: Number of patients with diabetes with A1c ≤6.5%
• Denominator: Total number of patients with diabetes on treatment sampled
• The specified achievable standard: ≥30% for primary care and ≥20% for tertiary care facilities

For other key performance indicators please refer to the Section on “Implementing The Guidelines”.

In Memory of Dr. Azura Dina Muhayidin
(1978-2015)
Al-Fatihah
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Type 2 Diabetes Mellitus (T2DM) is a prevalent non-communicable disease (NCD) which is increasing all over the world.

It is manifested by a chronic hyperglycaemic state in conjunction with other metabolic derangements.

T2DM is primarily due to insulin resistance as well as deficiency. The insulin resistance state results in increased hepatic glucose output, reduced utilisation of glucose by various organs, increased renal reabsorption of glucose and reduced incretin hormones production among others.

In general T2DM is an important risk factor for cardiovascular disease and results in various other complications namely nephropathy, retinopathy, neuropathy and dermatopathy.

Currently there is no known cure but the disease can be controlled enabling the individual to have an improved quality of life.

The main aim of management is directed at reducing acute and chronic complications (microvascular and macrovascular).

The National Health and Morbidity Survey (NHMS) 2011 reported diabetes prevalence figures of 15.2% and 20.8% for adults above the age of 18 and 30 years, respectively, in Malaysia. Among adults above the age of 18 years old, the prevalence was highest in the Indians (24.9%) followed by Malays (16.9%) and Chinese (13.8%). Of concern, 52% of those with diabetes above the age of 18 years old were unaware of their diagnosis. The percentage of undiagnosed diabetes is highest among the Malays (53%) followed by the Chinese (49%) and the Indians (42%). Similarly the proportion of undiagnosed diabetes is also highest in the young.

The prevalence of T2DM is increasing in the young with 2% and 4.9% of those between ages 18-19 years and 20-24 years, respectively, affected by it.

In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycaemic targets. Up to 21.4% of T2DM patients in primary care were on insulin compared to 65.4% in tertiary institutions. Majority are asymptomatic.

Common symptoms include increased thirst, polydipsia, polyuria, lethargy, weight loss, blurring of vision and increased risk of infection.
Complications

• Acute Complications
  a) Hypoglycaemia
  b) Hyperglycaemic states (e.g. diabetic ketoacidosis, hyperglycaemic hyperosmolar state)
  c) Microbial infections

• Chronic Complications
  a) Macrovascular (e.g. cardiovascular, cerebrovascular, peripheral vascular diseases)
  b) Microvascular (e.g. retinopathy, nephropathy, and neuropathy)

Management

• In principle, all patients with diabetes should undergo lifestyle modification, which consists of dietary therapy and increased physical activity.

• The need for oral medications or insulin therapy depends on the symptomatology, state of glycaemic control and the presence of any complications.
SECTION 2  SCREENING AND DIAGNOSIS

2.1 Objective
To detect pre-diabetes and diabetes among the general as well as high-risk populations, whilst ensuring timely appropriate intervention.

2.2 Strategy
• Screening the general population for at risk individuals.
• Screening of specific high-risk population e.g. those with history of gestational diabetes mellitus.

2.3 Who Should Be Screened
2.3.1 Symptomatic individuals
• Any individual who has symptoms suggestive of diabetes (tiredness, lethargy, polyuria, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) must be screened. 4 (Level III)

2.3.2 Asymptomatic individuals
Testing should be considered in all adults who are overweight or obese (BMI ≥23 kg/m² or have a waist circumference ≥80 cm for women and ≥90 cm for men), and have one or more of the following additional risk factors for diabetes:
• First-degree relative with diabetes
• History of cardiovascular disease (CVD)
• Hypertension (BP ≥140/90 mm Hg or on therapy for hypertension)
• Impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
• High density lipoprotein (HDL) cholesterol <0.9 mmol/L or triglycerides (TG) >2.8 mmol/L
• Other clinical conditions associated with insulin resistance (e.g. severe obesity and acanthosis nigricans)
• Women who delivered a baby weighing ≥4 kg or were diagnosed with gestational diabetes mellitus (GDM)
• Women with polycystic ovarian syndrome (PCOS)
• Physical inactivity
• Special populations (those who are receiving antiretroviral therapy 5 (Level II-1) or atypical antipsychotic drugs 6 (Level II-2))

* Modified from American Diabetes Association (ADA) Position Statement on Standards of Medical Care in Diabetes–2015. 4 (Level III)

In those without these risk factors, testing should begin at the age of 30 years. If tests are normal, screening should be done annually. 1 (Level II-2)

2.4 Screening Test
Screening can be done by measuring either venous or capillary blood using glucometer. Tests that can be performed are A1c, oral glucose tolerance test (OGTT), fasting blood glucose or random blood glucose.

Algorithm 1 is screening for symptomatic individuals and Algorithm 2 is for asymptomatic individuals. These algorithms also apply for adolescents.

Using A1c as a Screening Test for Diabetes
A1c is formed by a non-enzymatic glycation of haemoglobin. It reflects the average blood glucose level over the past 3 months. 7 (Level I) Measurement of glycated haemoglobin levels revealed that A1c assay showed the least variance in normal subjects compared to plasma glucose levels. 8 (Level II-2) Although
OGTT is the "gold standard" for diagnosing diabetes, it is known to be poorly reproducible and is cumbersome to perform.\(^9\) (Level II-2) Using A1c level to diagnose diabetes is convenient since therapeutic decisions are also based on this value, regardless of the findings of the OGTT.\(^8-13\) (Level II-2-3)

Based on the Metabolic Syndrome Study of Malaysia (MSSM) 2009 involving 4,400 adult population, an A1c level of 6.3% has a positive predictive value of 58% and negative predictive value of 84% (A1c at this level was found to give the maximal acceptable sum of specificity and sensitivity of 97% and 42.5%, respectively) in diagnosing diabetes for all three major ethnic groups in this country. Diagnosing diabetes based on A1c of 6.5% however leads to a lower unacceptable sensitivity of 36.7%. These data is based on correlation between A1c levels and 75-gram OGTT results where the receiver-operating characteristic (ROC) curve obtained was 0.85, consistent with other similar studies. Individuals with A1c between 5.6% and 6.2% will be deemed as having pre-diabetes. At A1c level of 5.6%, the sensitivity and specificity of diagnosing diabetes were 78% and 79% respectively. However, for a precise classification of abnormal glucose tolerance, individuals are recommended to undergo an OGTT.\(^14,15\) (Level II-2)

A1c results from patients with HbSS, HbCC, and HbSC must be interpreted with caution. These pathological conditions, including anaemia, increased red cell turnover, and transfusion requirements, may adversely affect A1c.\(^16\) (Level III)

Laboratories use many different methods for measuring A1c and some of these methods may give inaccurate results when the patient has a haemoglobin variant.\(^17\) (Level III) In patients suspected of having haemoglobinopathies, other screening tests should be used.

A1c is not appropriate for diagnosis of diabetes in:
1. Adolescents (<18 years old) since the diagnostic cut-off point was derived in those >18 years.
2. Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics.
3. Patients taking iron supplements (may falsely lower A1c levels).
4. Patients with acute pancreatic damage, including pancreatic surgery.
5. Presence of genetic, haematologic and illness-related factors that influence A1c and its measurement (e.g. haemoglobinopathies, rheumatoid arthritis, chronic liver disease, post-splenectomy).
6. Patients in chronic kidney disease (CKD) stage 4 or 5 and those on erythropoietin injections.
7. Anaemia due to iron, B12 or erythropoietin deficiencies.

### A1c Reporting and the New SI Units

Glycaemic control in patients with diabetes is assessed using A1c. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) clearly demonstrated the relationship of increasing A1c to the increase risk of complications.\(^18\) (Level I) Hence, for A1c to be useful, it is important that the A1c assays are standardised. Several international and national standardisation programs have evolved over the years to enable the comparability of A1c results from different laboratories to those reported in the DCCT trial.

In 1994, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Standardisation of A1c developed a global A1c reference system with a much improved intra-assay and inter-assay coefficients of variation of <2.5%.\(^19\) (Level II-1)

In Malaysia, recommendations have been made on the reporting of A1c results as IFCC-A1c values in SI units (mmol A1c/mol Hb) and National Glycohaemoglobin Standardization Program (NGSP-A1c) units (%) (Table 1).
Table 1: Conversion Table for A1c Between NGSP and IFCC Values

<table>
<thead>
<tr>
<th>NGSP-A1c (%)</th>
<th>IFCC-A1c (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>31</td>
</tr>
<tr>
<td>6.0</td>
<td>42</td>
</tr>
<tr>
<td>6.5</td>
<td>48</td>
</tr>
<tr>
<td>7.0</td>
<td>53</td>
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</tr>
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<td>9.0</td>
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<td>10.0</td>
<td>86</td>
</tr>
<tr>
<td>11.0</td>
<td>97</td>
</tr>
<tr>
<td>12.0</td>
<td>108</td>
</tr>
</tbody>
</table>

NGSP = National Glycohaemoglobin Standardization Program; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine

- Above NGSP-A1c level of 5%, every 1% increment is equivalent to 11 units (mmol/mol) in the IFCC-A1c.
- Conversion: A1c (mmol/mol) = [10.93 x A1c (%)] - 23.5

Algorithm 1: Screening for T2DM in Symptomatic Individuals

WITH SYMPTOMS

Venous Plasma Glucose

<table>
<thead>
<tr>
<th>Fasting</th>
<th>Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0</td>
<td>≥7.0</td>
</tr>
<tr>
<td>≥11.1</td>
<td>&lt;11.1</td>
</tr>
</tbody>
</table>

OGTT

Type 2 Diabetes Mellitus

* All values are in mmol/L
Algorithm 2: Screening for T2DM in Asymptomatic Individuals

** Algorithm Diagram **

1. Capillary Random Blood Glucose
2. Venous FPG
3. Venous RPG
4. OGTT
5. DM
6. IFG
7. IGT
8. DM

* All values are in mmol/L.
** FPG = fasting plasma glucose; RPG = random plasma glucose; OGTT = oral glucose tolerance test; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; DM = diabetes mellitus.

- If FPG \( \geq 7.0 \) mmol/L or 2-hour PPG \( \geq 11.1 \) mmol/L, a repeat glucose value (fasting or random) or A1c can be used to make the diagnosis of diabetes.
- For diagnosis of T2DM, venous plasma glucose value is required.

2.5 Schedule
Screening should be done annually in those who are listed in 2.3.2.

2.6 Diagnosis
Diagnosis must be confirmed by measurement of venous plasma glucose or A1c level. Venous sample for plasma glucose and A1c should be taken prior to initiating therapy.

Table 2: Diagnostic Value for T2DM Based on Venous Plasma Glucose

<table>
<thead>
<tr>
<th>Venous Plasma Glucose</th>
<th>Fasting</th>
<th>Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 7.0 ) mmol/L</td>
<td>( \geq 7.0 ) mmol/L</td>
<td>( \geq 11.1 ) mmol/L</td>
</tr>
</tbody>
</table>

- In symptomatic individual, one abnormal glucose value is diagnostic.
- In asymptomatic individual, 2 abnormal glucose values are required.
Table 3: Diagnostic Values for Glucose Intolerance and T2DM Based on OGTT

<table>
<thead>
<tr>
<th>Category</th>
<th>0-hour</th>
<th>2-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;6.1</td>
<td>&lt;7.8</td>
</tr>
<tr>
<td>IFG</td>
<td>6.1–6.9</td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>-</td>
<td>7.8–11.0</td>
</tr>
<tr>
<td>DM</td>
<td>≥7.0</td>
<td>≥11.1</td>
</tr>
</tbody>
</table>

- IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus
- In adolescents, the glucose load in OGTT is based on body weight (1.75 g/kg body weight, maximum of 75 g).

Table 4: Diagnostic Values for Pre-diabetes and T2DM Based on A1c

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>&lt;5.6% (38 mmol/mol)</td>
<td>5.6-6.2% (38-44 mmol/mol)</td>
<td>≥6.3% (45 mmol/mol)</td>
</tr>
</tbody>
</table>

- A repeat A1c should be done 4 weeks after the first positive test for asymptomatic patients.
- For symptomatic patients, a single positive test is sufficient.

2.7 Cardiovascular Risk Estimation

In general, patients with pre-diabetes and T2DM have 2-3 fold increased risk of developing cardiovascular disease. Sixty percent of patients with diabetes will eventually die from cardiovascular complications.

As such, it is prudent that the cardiovascular risk profiles be determined at diagnosis of pre-diabetes and diabetes. It is recommended to perform cardiovascular risk assessment using either one of the following two tools:

- Framingham Risk Score (FRS)
- Systematic COronary Risk Evaluation (SCORE)-high model (validated only for men)

The above two CVD risk-stratifying tools have been validated in Malaysia using the NHMS II and III cohorts in adults aged between 40 and 65 years.

Those who are in the high-risk group should have their T2DM and other CVD risk factors treated aggressively with closer monitoring.

**Recommendations: Screening and Diagnosis**

1. Screening for diabetes using fasting plasma glucose (FPG) or A1c should be performed annually in those with risk factors and those ≥30 years. [Grade C]
2. More frequent and/or earlier testing with either a FPG or 2-hour plasma glucose in a 75-g OGTT or A1c should be considered in people with additional risk factors for diabetes. [Grade C]
3. Testing with a 75-g OGTT should be considered in individuals with a FPG of ≥6.1 to 6.9 mmol/L or A1c between 5.6 to 6.2% in order to identify individuals with IGT or diabetes. [Grade C]
4. Diagnosis of diabetes and pre-diabetes can be made using fasting glucose, random glucose, OGTT or A1c. [Grade B]
5. At diagnosis of pre-diabetes and diabetes, it is recommended to perform cardiovascular risk assessment using either FRS or SCORE-high model. [Grade B]
3.1 Initial Assessment
At diagnosis, a detailed history, full physical examination (including fundoscopy and monofilament test) and baseline investigations must be done to assess the CVD risk factors and complications of diabetes.

Management should be based on the initial assessment and baseline investigations.

Diabetes management involves lifestyle modification, medications and patient education to encourage self-care and empowerment. 22,23 (Level III), 24,25 (Level I)

Table 5: History Taking

<table>
<thead>
<tr>
<th>Specific symptoms</th>
<th>Increased thirst, polydipsia, polyphagia, polyuria, nocturia, malaise, fatigue, weight loss, altered vision and frequent infections.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition to diabetes</td>
<td>Age over 30 years, family history, ethnic group, overweight, physical inactivity, hypertension, obstetric history of large babies or gestational diabetes, medications causing hyperglycaemia</td>
</tr>
<tr>
<td>Risk factors for complications</td>
<td>Personal or family history of CVD, smoking, hypertension, dyslipidaemia and end-stage renal disease (ESRD).</td>
</tr>
<tr>
<td>General symptoms review</td>
<td>Cardiovascular symptoms, neurological symptoms, foot and toe problems, recurrent infections (especially urinary and skin), bladder, sexual dysfunction and depressive symptoms.</td>
</tr>
<tr>
<td>Lifestyle issues</td>
<td>Smoking, alcohol, occupation, dietary habits and physical activity</td>
</tr>
</tbody>
</table>

Table 6: Physical Examination

<table>
<thead>
<tr>
<th>Weight/waist</th>
<th>Body mass index (BMI) = weight (kg) / height² (m²), waist circumference (WC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>Blood pressure (lying and standing), neck and peripheral pulses, precordial examination</td>
</tr>
<tr>
<td>Eye</td>
<td>Visual acuity (with corrected vision), cataract, retinopathy (examine with pupils dilated)</td>
</tr>
<tr>
<td>Feet</td>
<td>Sensation, skin condition, pressure areas, interdigital lesions, and bone deformities</td>
</tr>
<tr>
<td>Peripheral nerves</td>
<td>Tendon reflexes</td>
</tr>
<tr>
<td></td>
<td>Sensation: touch (e.g: with 10-g monofilament), vibration (e.g. with 128-Hz tuning fork)</td>
</tr>
</tbody>
</table>

Table 7: Investigations

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Fasting plasma glucose (FPG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>Renal profile</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Liver function test</td>
</tr>
<tr>
<td>Urinalysis for albumin, microalbuminuria if albuminuria is absent</td>
<td>ECG</td>
</tr>
</tbody>
</table>
Aims of Treatment

- The overall aims of management are to improve quality of life, reduce complications and prevent premature death. Patient and family members should be counselled by identifying and addressing concerns which may cause distress thus adversely affecting management.

a) Short term:
- Relieve of symptoms and acute complications

b) Long term:
- Achievement of appropriate glycaemic levels
- Reduction of concurrent risk factors
- Identification and treatment of chronic complications

- Most of the microvascular complications of diabetes are related to the degree and the length of exposure to hyperglycaemia. Data from the follow up studies of the DCCT-EDIC and UKPDS emphasised the role of glycaemic control early in the course of the disease and its value in the prevention of later complications. 26,27 (Level I)

- The phenomenon of continuing beneficial effect on the rate of developing diabetic complications after a period of improved glycaemic control even if followed by a return to usual (often poorer) metabolic control has been described as representing a legacy effect or metabolic memory. 26,27 (Level I) The significance of this legacy effect should be emphasised to all newly diagnosed diabetic patients.

3.2 Diabetes Education

- Diabetes education is effective in improving clinical outcomes and quality of life. Hence it should be advocated to all patients with T2DM regardless of their treatment mode. 28-30 (Level I) Their family members and carers should be involved as well.

- The more the duration of contact time between the educator and the patient, the better the A1c reduction. 28 (Level II-1)

- A face-to-face delivery, cognitive reframing teaching method (a psychological technique that consists of identifying and then discussing the issues that impairs the person's ability to adjust to particular situations in this case the idea of having T2DM) and exercise content were more likely to improve glycaemic control. 28 (Level II-1)

- Periodic reinforcement of the diabetes education such as coaching via monthly telephone calls improves glycaemic control and compliance to complication screening. Interventions that encourage patient’s active participation such as patient empowering group education and automatic telephone management program resulted in better outcomes. 31,32 (Level I), 33 (Level II-1)
Table 8: Contents of Education: 20,22 (Level II-2), 34,35 (Level I), 36 (Level II-2), 37,38 (Level III)

<table>
<thead>
<tr>
<th>Contents / Scope of Education</th>
<th>Contents / Scope of Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diet</td>
<td>• Stop smoking</td>
</tr>
<tr>
<td>• Food exchanges</td>
<td>• Problem solving skills e.g. management of hypoglycaemia, sick days</td>
</tr>
<tr>
<td>• Exercise</td>
<td>• Psychosocial adaptation to diabetes e.g. to manage the stress associated with the initial diagnosis of diabetes or its complications and initiation of insulin</td>
</tr>
<tr>
<td>• Medication</td>
<td></td>
</tr>
<tr>
<td>• Complications (acute and chronic)</td>
<td></td>
</tr>
<tr>
<td>• Self-care/SMBG/foot care</td>
<td></td>
</tr>
</tbody>
</table>

Algorithm 3: Education Strategies

- Health education, diet therapy, exercise and compliance to medications must be reinforced at follow-up. 24,30 (Level I)

3.3 Team Approach

Consider referral to diabetes educator and dietitian for consolidation of education. In the team management of diabetes the patient is the core member.

For the patient to accept responsibility for self-care they must understand the disease, its effect on health and the necessity of management. Good communication between team members is important so that advice is consistent and not confusing for the patient.

The following professionals are important team members in the multi-disciplinary management of diabetes:

- **Primary Care Practitioner**
  Primary care practitioner plays a central role in coordinating management of person with diabetes and in providing patient education as well as counseling. Primary care practitioner is the first point of contact with people with diabetes and usually assumes the responsibility for their overall management.
In some instances where the diabetes educator or dietitian is not available, primary care practitioner or the paramedics must undertake the responsibility to give detailed education to the patient.

**Diabetes Educator**
The diabetes educator often spend more time than the primary care practitioner in facilitating knowledge and skills regarding healthy eating, physical activity, self-monitoring, medication usage, setting goal, problem solving, risk reduction practices such as foot care, smoking cessation and keeping with medical appointment.

**Dietitian**
The role of the dietitian in the management of diabetes is paramount. Lifestyle changes alone (healthy food and regular exercise with ensuing weight loss) are sufficient for glycaemic control in the majority of patients with newly diagnosed T2DM. Recommendation should be individualised to maximise cooperation. Referral to a dietitian is desirable to ensure detailed education on this important aspect of management. The other team members must understand the principles of dietary advice to reinforce the dietary recommendations for the patient.

**Physician/Endocrinologist/Diabetologist**
The advice of a specialist physician may be valuable for patients with complicated problems related to diabetes. These may be in the form of poor diabetes control despite the standard care and the onset of various complications. A shared care approach by the primary care practitioner and specialist will provide the best combination of expertise and continuity of care to the patient.

**Pharmacist**
Pharmacists play a role in ensuring adherence and giving information about medications action and side effects. They may undertake special tasks of training the patients to administer and adjust insulin dosing.

**Ophthalmologist/Optometrist**
Referral to an ophthalmologist/optometrist is required for further assessment and management of retinopathy and other eye problems.

**Oral Health Professional**
Dental and periodontal problems are common in patients with diabetes. They tend to have poorer oral hygiene and more severe gingival and periodontal diseases. These may contribute to worsening of glycaemic control. Patients with diabetes should be advised to see a dentist regularly.

### Recommendations: Diabetes Education

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All patients should be given diabetes education.</td>
<td>A</td>
</tr>
<tr>
<td>2. The type of education, content, duration and revision frequencies should depend on the need of the patients and the resources at the health care centre.</td>
<td>C</td>
</tr>
<tr>
<td>3. All newly diagnosed T2DM need to be reviewed by a medical doctor in which screening for other cardiovascular risks need to be carried out.</td>
<td>C</td>
</tr>
<tr>
<td>4. The significance of the legacy effects and metabolic memory should be emphasised to all newly diagnosed diabetic patients.</td>
<td>A</td>
</tr>
</tbody>
</table>
3.4 Targets for Control

Table 9: Targets for Control of Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycaemic control*</td>
<td>Fasting or pre-prandial 4.4–7.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Post-prandial** 4.4–8.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td>A1c++ ≤6.5%</td>
</tr>
<tr>
<td>Lipids</td>
<td>Triglycerides ≤1.7 mmol/L</td>
</tr>
<tr>
<td></td>
<td>HDL-cholesterol &gt;1.0 mmol/L (male)</td>
</tr>
<tr>
<td></td>
<td>&gt;1.2 mmol/L (female)</td>
</tr>
<tr>
<td></td>
<td>LDL-cholesterol ≤2.6 mmol/L#</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤135/75 mm Hg§</td>
</tr>
<tr>
<td>Exercise</td>
<td>150 minutes/week</td>
</tr>
<tr>
<td>Body weight*</td>
<td>If overweight or obese, aim for 5-10% weight loss in 6 months</td>
</tr>
</tbody>
</table>

* Modified from the NICE guideline: Type 2 diabetes: The management of type 2 diabetes, 2009. 46 (Level III)
Glycaemic target should be individualised to minimise risk of hypoglycaemia. 43 (Level I) The committee acknowledges the increased CVD death in the intensive group of the ACCORD study. 43 (Level I) However, the committee believes it is due to the overall treatment strategies that were employed to achieve the A1c target rather than the reduction in A1c. This is also collaborated by the ADVANCE study. 41,47 (Level I)

** Measured at least 90 minutes after meals.

++ A1c ≤6.5% is advocated for patients with a shorter duration of diabetes, no evidence of significant CVD and longer life expectancy and have minimal risk of hypoglycaemia. There are strong benefits for reduction of nephropathy (ADVANCE) and retinopathy (ACCORD/ACCORD Eye Study Group) at or below this level of A1c. 41,48 (Level I)

# In individuals with overt CVD, LDL cholesterol target is <1.8 mmol/L.

§ In children and adolescents, blood pressure (BP) should be <95th percentile for age and sex. 49 (Level III)

Table 10: A1c Targets

<table>
<thead>
<tr>
<th>Individualised A1c Targets and Patients’ Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tight (6.0–6.5%)</td>
</tr>
<tr>
<td>• Newly diagnosed</td>
</tr>
<tr>
<td>• Younger age</td>
</tr>
<tr>
<td>• Healthier (long life expectancy, no CVD complications)</td>
</tr>
<tr>
<td>• Low risk of hypoglycaemia</td>
</tr>
</tbody>
</table>

• Modified from Management of Hyperglycaemia in Type 2 Diabetes: A Patient-Centered Approach: A Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), 2012. 50 (Level III)

3.5 Lifestyle Modification

3.5.1 Medical Nutrition Therapy
Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and delaying complications. Proper diet is crucial at any stage of management of diabetes including those on medication.

The goals of MNT together with medication are to attain and maintain blood glucose, blood pressure and
lipid profile as close to normal as safely as possible. These goals can be achieved through healthy food choices.

General Recommendations

• Nutrition care by a dietitian should be provided under the following conditions: at diagnosis, sub-optimal metabolic and/or weight control, at initiation of insulin therapy, development of other comorbidities such as hyperlipidaemia, hypertension and chronic kidney disease. 51 (Level I)

• Diet counseling is effective to help lower A1c by an average of 1–2%. 52 (Level I) Patients who have diabetes should receive individualised nutrition care from a dietitian to achieve treatment goals. 53 (Level I)

• Dietary counseling should be individualised according to nutritional needs, severity of disease, cultural preferences and willingness to change. 51 (Level III)

Specific Recommendations

• Prevention of Diabetes:
  a) Weight loss of 5-10% of initial body weight over a 6-month period is recommended for all overweight or obese patients who have or at risk for diabetes. 44,45 (Level I)

This can be achieved by:

i. A reduced calorie diet. Standard weight-loss diets reduce daily energy by 500–1,000 kcal to achieve an initial weight loss of 0.5–1.0 kg per week. 54 (Level I)

ii. Physical activity of 150 minutes per week i.e. 30 minutes five days or more per week. 55 (Level I)

iii. A combination of reduced calorie diet, physical activity and behaviour modification can provide greater initial weight loss. 55 (Level I)

iv. Meal replacements (MRPs) can be used as part of a comprehensive meal plan for weight loss and weight maintenance. 56 (Level I)

b) There is no ideal percentage of energy for carbohydrate, protein and fat for diabetes. A balanced diet consisting of 45–60% energy from carbohydrate, 15–20% energy from protein and 25–35% energy from fat are encouraged. 57 (Level III) These recommendations must be individualised based on weight, glycaemic and other metabolic goals, cultural preferences and individual lifestyle.

c) A high dietary fibre diet is encouraged for the prevention of diabetes. A high fibre diet (20–30 g fibre/day) consisting of vegetables, fruits, legumes and whole grain cereals is encouraged. 58 (Level II-2)

d) Whole grains should form 50% of the total grain intake as recommended by the Malaysian Dietary Guidelines, 2010. Higher consumption of whole grains can contribute to the prevention of T2DM. 58 (Level II-2)

e) Limit consumption of sugar-sweetened beverages (SSB) to less than 2 servings a day or about 10% of total daily caloric intake for prevention of diabetes and weight gain. 59,60 (Level II-2)

• Management of Diabetes

In addition to the above recommendations:

a) Total carbohydrate (CHO) intake should be monitored in patients with T2DM. 61 (Level I)

i. Total CHO intake can be monitored by using grams, exchange list, household or hand measures as long as it is practical for patients to comprehend and follow. Please refer to APPENDIX 1 and APPENDIX 2.

ii. CHO intake must be kept consistent on a day-to-day basis if patient is on diet therapy alone, oral anti-diabetic agents (OADs) or fixed insulin regime.

iii. It is prudent to individualise the distribution of the total CHO exchanges allowed in a day into meals according to the patient’s lifestyle.
iv. If patient is adjusting their meal-time insulin doses or on insulin pump (i.e. flexible insulin) consistency is not required. Insulin doses should be adjusted to match CHO intake. Self-monitoring of blood glucose is essential to adjust CHO intake and insulin dose.

v. A minimum of 130 g/day CHO should be provided to ensure adequate intake of fibre, vitamins, and minerals, as well as to prevent ketosis and to provide dietary palatability. 

vi. Sucrose (e.g. table sugar) intake must be counted as part of the total carbohydrate intake. Excess sucrose intake contributes to calories and may cause weight gain.

vii. Non-nutritive sweeteners do not impact glycaemic level. Intake should not exceed acceptable daily intake (ADI) levels.

b) In patients with normal renal function, usual protein intake of 15–20% energy has minimal effect on glycaemic control. It is recommended to include lean sources of protein such as lean meat, fish, chicken/poultry without skin and soy protein. In patients with impaired renal function, protein restriction of 0.8–1.0 g/kg body weight/day may be recommended.

c) Patients with diabetes should limit total fat (25–35% energy intake), saturated fats (<7% energy intake), minimal trans fat (<1% energy intake) and dietary cholesterol (<200 mg/day) for prevention and treatment of cardiovascular disease.

i. Saturated fats are usually found in animal fats (skin of poultry, fatty meats, full cream dairy products) and coconut milk.

ii. A healthy diet incorporating oats, nuts and legumes, green leafy vegetables and soy protein may be beneficial for cardiovascular health.

d) In normotensive and hypertensive patients, a reduced sodium intake (<2,000 mg sodium/day or 5 g of salt a day or 1 teaspoon) with a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure.

Sodium restriction can be achieved through avoiding high sodium foods (soya sauce, ketchup and other sauces, premixed cooking paste, monosodium glutamate, salt preserved foods and processed foods), reducing the frequency of eating out and limiting salt in cooking to ¼ to ½ teaspoonful of salt per person per day.

e) Patients with diabetes have the same vitamin and mineral requirements as the general population. There is no clear evidence of benefit from the use of antioxidant vitamins A, C, E, selenium, herbs and omega-3 fatty acids in diabetes management.

f) Patients with diabetes do not require special oral nutritional supplement beverages unless malnourished, have not been eating well for prolonged periods of time or used as meal replacements for weight loss.

3.5.2 Low Glycaemic Index Diet

- Monitoring total CHO intake remains a key strategy in achieving glycaemic control.
- Both the amount and type of carbohydrates in food do affect blood glucose levels. The type of CHO is best described using the Glycaemic Index (GI) concept.

a) Glycaemic index (GI) is a measure to classify type of CHO based on their effect on the blood glucose level. It is a ranking system that indicate how quickly CHO food raises blood glucose
Food with high GI value raises blood glucose more than food with medium or low GI. Please refer to Appendix 3.

b) Substituting high GI foods with lower GI foods at mealtime reduces postprandial blood glucose level 73-76 (Level I) and modestly improve glycaemic control 73-76 (Level II-2) by reduction of A1c between 0.14% and 0.5%, provided the energy and total CHO intake are not excessive.

<table>
<thead>
<tr>
<th>Recommendations: Medical Nutrition Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Medical nutritional therapy is the mainstay of prevention and treatment of T2DM. [Grade A]</td>
</tr>
<tr>
<td>2. For obese and overweight patients, weight loss of 5–10% of initial body weight over a 6-month period is recommended to prevent T2DM. [Grade A]</td>
</tr>
<tr>
<td>3. A balanced diet consisting of 45–60% energy from carbohydrate, 15–20% energy from protein and 25–35% energy from fats are encouraged. [Grade C]</td>
</tr>
<tr>
<td>4. Substituting high GI foods with lower GI foods at mealtime reduces postprandial blood glucose. [Grade A]</td>
</tr>
</tbody>
</table>

3.5.3 Physical Activity
Increased physical activity can improve glycaemic control, assist with weight maintenance, and reduce the risk of CVD. 35 (Level I) Combining physical activity with dietary intervention results in greater A1c reduction.

Mild to moderate exercise is generally safe but before beginning a program of vigorous physical activity, people with diabetes should be assessed for complications that may preclude vigorous exercise (CVD, retinopathy, neuropathy and foot injury). 77 (Level II-2) In older patients, previously sedentary, long-standing diabetes, patients with multiple risk factors, and patients with previous evidence of atherosclerotic disease should be considered for pre-exercise assessment as shown in Appendix 4.

The patient should choose an activity that he or she is likely to maintain. Walking is accessible to most patients in terms of time and financial expenditure.

General Recommendations
- Individuals should exercise 5 days a week, preferably most days of the week and with no more than 2 consecutive days without physical activity. 34 (Level I)
- For patients with T2DM, supervised exercise programs have been particularly effective in improving glycaemic control, reducing the need for OADs and insulin, and producing modest but sustained weight loss. 78,79 (Level I)
- Both aerobic and resistance exercise are beneficial for patients with diabetes, and it is optimal to do both types of exercise. The duration of exercise should be at least 150 minutes/week of moderate-intensity aerobic physical activity and/or at least 90 minutes/week of vigorous aerobic 34 (Level I) and at least two sessions per week of resistance exercise. Please refer to Appendix 5 for examples of exercise.
- Overweight and obese individuals should gradually increase physical activity to 60–90 minutes per day for long term weight loss.
- Any increase in daily energy expenditure is beneficial e.g. gardening, walking up stairs, washing the car, or mopping the floor.
In order to prevent hypoglycaemia, medication doses can be reduced or extra carbohydrate can be consumed before or during physical activity.

**Recommendations: Physical Activity**

1. The duration of exercise should be at least 150 minutes/week of moderate-intensity and/or at least 90 minutes/week of vigorous aerobic and at least two sessions per week of resistance exercise. [Grade A]
2. Anti-diabetic agent(s) may need adjustment if exercise is planned. [Grade C]

### 3.6 Medications

#### 3.6.1 Oral Anti-diabetic (OAD) Agents

**a) Biguanides (Metformin)**

- Metformin lowers blood glucose especially fasting blood glucose by decreasing hepatic glucose production and does not stimulate insulin secretion, thus on its own it is usually not accompanied by hypoglycaemia.
- Metformin reduces A1c by about 1.5%. 80 (Level I)
- Usage in combination with other OAD agents have a synergistic effect to further reduce blood glucose and may reduce insulin requirements.
- Most common adverse effects are nausea, anorexia and diarrhoea. These are minimised if metformin is taken together with/or after meals. To reduce gastrointestinal side effects, it is best to start with a single daily dose, followed by weekly titration. Extended release formulation also reduces these side effects. 80 (Level I)
- One of the complications of long term metformin therapy is vitamin B12 deficiency.
- Lactic acidosis is rare (<1 case per 100,000 treated patients) and usually associated with renal impairment. 81 (Level I)
- One of the benefits of metformin is either weight stability or mild weight loss.
- Dose beyond 2000 mg OD does not confer any further glycaemic benefit and significantly increase gastrointestinal side effects.
- Low dose metformin can be safely prescribed to lactating mothers. 82 (Level II-2)

**Table 11: Metformin Formulations and Dosage**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>500 mg</td>
<td>Initial dose 500 mg OD</td>
<td>1000 mg TDS</td>
</tr>
<tr>
<td>Metformin SR</td>
<td>850 mg</td>
<td>Usual dose 1500 mg OD</td>
<td>850 mg TDS</td>
</tr>
<tr>
<td>Metformin XR</td>
<td>500 mg / 750 mg</td>
<td>Initial dose 500 mg OD</td>
<td>2000 mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual dose 850 mg BD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual dose 2000 mg OD</td>
<td></td>
</tr>
</tbody>
</table>

- For fixed combination formulations, please refer to specific product inserts.

**b) Sulphonylureas (SUs)**

- SUs reduce plasma glucose by increasing insulin secretion with an average A1c reduction of 0.4-1.6%. 83 (Level I)
- The major adverse effect is hypoglycaemia. The risk is higher in renal impairment, liver cirrhosis and the elderly.
- Weight gain in the range of 1.5–2.5 kg is common.
• Among the second generation SUs, gliclazide and glimepiride are preferred over other SUs as they cause less risk of hypoglycaemia and less weight gain.  
84,85 (Level I), 86 (Level III)

• Glibenclamide has been shown to be associated with significant risk of hypoglycaemia and WHO recommends against its use in those above 60 years of age. 87 (Level I)

• SUs are highly protein bound. Administration of drugs that can displace them (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), anti-thyroid drugs, sulpha drugs, anticoagulants and α-blockers) can increase the risk of hypoglycaemia.

• SUs should be taken 30 minutes before meals and can be combined with other OAD agents to improve glucose control.

Table 12: SU Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide</td>
<td>5 mg</td>
<td>2.5 mg OD</td>
<td>10 mg BD</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80 mg</td>
<td>40 mg OM</td>
<td>160 mg BD</td>
</tr>
<tr>
<td>Gliclazide MR</td>
<td>60 mg</td>
<td>30 mg OM</td>
<td>120 mg OM</td>
</tr>
<tr>
<td>Glipizide</td>
<td>5 mg</td>
<td>2.5 mg OM</td>
<td>10 mg BD</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>2 mg / 3 mg</td>
<td>1 mg OM</td>
<td>6 mg OM</td>
</tr>
</tbody>
</table>

• For fixed combination formulations, please refer to specific product inserts.

Note:
Glibenclamide is metabolised by the liver but its metabolites are active and excreted by the kidney. The drug should be stopped if renal impairment develops. Other second generation SUs (glimepiride, gliclazide and glipizide) may still be used with caution.

c) Meglitinides

• These are short acting insulin secretagogues that bind to a different site within the SU receptor.

• It has a shorter half-life than SUs, and is rapidly absorbed from the gastrointestinal tract with peak levels 1-hour post administration and eliminated within 4–6 hours. 88 (Level I)

• It should be taken within 10 minutes before main meals.

• It reduces A1c by 1.0–1.2%. 88 (Level I)

• It can be added to other OAD(s) except SU.

• It is associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent.

• It is primarily used to control postprandial hyperglycaemia (PPG). 88 (Level I)

Table 13: Meglitinides Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>0.5 mg / 1 mg / 2 mg</td>
<td>0.5 mg with main meals</td>
<td>4 mg with main meals (not exceeding 16 mg daily)</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>120 mg</td>
<td>60 mg with main meals</td>
<td>120 mg with main meals (not exceeding 360 mg daily)</td>
</tr>
</tbody>
</table>

Caution:
There is a higher risk of prolonged hypoglycaemia when repaglinide is combined with gemfibrozil. 89 (Level I)
This combination is contraindicated.

d) Alpha-Glucosidase Inhibitors (AGIs)

• AGIs e.g. acarbose reduces the rate of absorption of polysaccharides in the proximal small intestine by inhibiting α-glucosidase enzymes. They should be taken with main meals. 90 (Level I)
• It lowers postprandial glucose without causing hypoglycaemia.
• It is less effective in lowering glycaemia than metformin or SU, reducing A1c by 0.5–0.8%. \(^90\) (Level I)
• It has synergistic effects when used with other OAD(s) and may be combined with insulin.
• The commonest side effects are bloating, abdominal discomfort, diarrhoea and flatulence. \(^90\) (Level I)

Table 14: AGIs Formulation and Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>50 mg / 100 mg</td>
<td>Initial dose 50 mg OD</td>
<td>100 mg TDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usual dose 50–100 mg during main meals</td>
<td></td>
</tr>
</tbody>
</table>

e) Thiazolidinediones (TZDs)
• Thiazolidinediones are peroxisome proliferator-activated receptor-gamma (PPAR-\(\gamma\)) agonists and act primarily by increasing insulin sensitivity in muscle, adipose tissue and liver.
• TZDs reduce A1c by 0.5–1.4%. \(^91\)-\(^95\) (Level I)
• Improvement in glycaemic control may only be seen after six weeks with maximum effect at six months.
• They can be combined with other OAD(s).
• Side effects include weight gain (due to redistribution of body fat), fluid retention, heart failure, macular oedema and osteoporosis.
• The majority of fractures associated with TZD use were in the distal upper or lower limb, as opposed to the classic sites of osteoporotic fractures. \(^96\) (Level I), \(^97\) (Level II-2)
• TZDs are contraindicated in patients with CCF \(^98\) (Level I) and liver failure.
• Use of TZDs as first line therapy has been found to have greater durability in glycaemic control compared to metformin and sulphonylurea (SU). \(^96\) (Level I)

Table 15: TZD Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>4 mg / 8 mg</td>
<td>4 mg OD</td>
<td>8 mg OD</td>
</tr>
<tr>
<td>Plioglitazone</td>
<td>15 mg / 30 mg</td>
<td>15 mg OD</td>
<td>45 mg OD</td>
</tr>
</tbody>
</table>

• For fixed combination formulations, please refer to specific product inserts.

NOTE: Incretin Effect
• After meals, incretins [glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinothetic polypeptide (GIP)] \(^99\) (Level II-1), \(^100\) (Level I) are released; these augment glucose-induced insulin secretion and suppress glucagon release thus reducing hepatic glucose output in a glucose dependent manner.
• Other than the above two actions, incretins also reduce gastric motility (thus slowing glucose absorption) and increase satiety by acting on centres in the brain.
• The incretin effect is markedly decreased in T2DM, \(^101\) (Level II-2) resulting in delayed and reduced insulin release as well as lack of suppression of glucagon release after a meal.
• Agents that increase the effect of incretins have been proven to improve glucose control - 2 classes of drugs have recently been developed: DPP-4 inhibitor (incretin enhancer) and GLP-1 analogue or GLP-1 receptor agonist (incretin mimetic).
• In normoglycaemic state, these agents do not stimulate insulin secretion neither does it suppress glucagon release. \(^99\) (Level II-1), \(^100\) (Level I)
f) Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

• It lowers A1c by 0.5–0.8%, 102-107 (Level I) and can be combined with other OAD(s).
• It is weight neutral and has minimal risk of hypoglycaemia. 108-112 (Level I)
• It’s efficacy is not influenced by the duration of T2DM. 102-107 (Level I)
• The SAVOR-TIMI 53 clinical trial has shown that the use of saxagliptin is associated with increased risk for hospital admission for heart failure. 113 (Level I)
• The more recent TECOS study did not show any increased risk of hospitalisation for heart failure. 114 (Level I)
• In general, the use of DPP-4 inhibitors is not associated with any adverse cardiovascular outcomes. 113-115 (Level I)

Table 16: DPP-4 Inhibitors Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>25 mg / 50 mg / 100 mg</td>
<td>25 mg OD</td>
<td>100 mg OD</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg</td>
<td>25 mg BD</td>
<td>50 mg BD</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg / 5 mg</td>
<td>2.5 mg OD</td>
<td>5 mg OD</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg</td>
<td>5 mg OD</td>
<td>5 mg OD</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>6.25 mg / 12.5 mg / 25 mg</td>
<td>6.25 mg OD</td>
<td>25 mg OD</td>
</tr>
</tbody>
</table>

• For fixed combination formulations, please refer to specific product inserts.

g) Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors

• This class of drugs selectively inhibits SGLT2, a transporter in the proximal tubule, thus reducing glucose reabsorption leading to an increase in urinary glucose excretion. 116-119 (Level I)
• It reduces A1c by 0.2% to 0.8%. 120 (Level I)
• This is accompanied by weight loss (2.5 to 3.0 kg) 120 (Level I) and modest blood pressure reduction together with lower risk of hypoglycaemia.
• It is not recommended for those on concomitant treatment with loop diuretic.
• Efficacy of SGLT2-i is dependent on renal function and it is not recommended in patients with moderate to severe renal impairment (e-GFR <60 mL/min/1.73 m²)
• It can be combined with other OAD(s) to improve glucose control.
• SGLT2 inhibitor has been shown to increase glucagon level and combining it with DPP-4 inhibitor will compensate this.
• Side effects include significant increased of genitalia and urinary tract infection.
• The US FDA has issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture. 121 (Level III)
• A few cases of euglycaemic diabetic ketoacidosis (DKA) had been reported in patients who were on SGLT2 inhibitors and caution should be exercised when prescribing these agents in those with severe beta-cell insufficiency, latent autoimmune diabetes and in postsurgical patients. 122 (Level III)
• The EMPA-REG clinical trial conducted in patients with T2DM at high risk for cardiovascular events showed a lower rate of cardiovascular events and all-cause mortality. 123 (Level I) The reasons behind these findings are yet to be determined.
Table 17: SGLT2 Inhibitors Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>5 mg / 10 mg</td>
<td>5 mg OD</td>
<td>10 mg OD</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>100 mg / 300 mg</td>
<td>100 mg OD</td>
<td>300 mg OD</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg / 25 mg</td>
<td>10 mg OD</td>
<td>25 mg OD</td>
</tr>
</tbody>
</table>

3.6.2 Injectable Agents

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists \(^{124}\) (Level I)

**Exenatide**

- There are two forms of exenatide available: immediate release (IR) and extended release (XR) formulations. \(^{125}\) (Level I)
- It is given subcutaneously. The IR formulation is given twice daily just before breakfast and dinner. The XR formulation can be given at any time of day with or without meals. \(^{128,129}\) (Level I)
- Exenatide IR formulation reduces A1c by 0.5–1.0% \(^{126}\) (Level I) as add on to metformin \(^{127}\) (Level I) and/or SU. \(^{128,129}\) (Level I)
- In patients who are on combination of metformin and SU with an A1c <10.0%, the addition of exenatide produced similar glycaemic improvement compared to insulin glargine without any increase risk of hypoglycaemia and weight gain. \(^{130}\) (Level I)
- Exenatide XR give a significant advantage in reduction of A1c and fasting blood sugar but not postprandial glucose levels compared to exenatide IR with comparable weight loss of between 4–4.5 kg. \(^{131}\) (Level I)
- Exenatide weekly in combination with OAD(s) reduces A1c up to 1.5%. \(^{132}\) (Level I)
- Progressive weight loss is seen \(^{127-129}\) (Level I) because of its effect on satiety and delay in gastric emptying. \(^{133,134}\) (Level II-1), \(^{135}\) (Level I)
- The main adverse effects are gastrointestinal symptoms, notably nausea which can be minimised by starting at a low dose with up-titration after a month. \(^{136}\) (Level I)
- It should be stored in the refrigerator (36 to 46°F [2 to 8°C]).
- It can be administered in the abdomen, thigh, or upper arm on a rotating basis.
- Exenatide should not be used in patients with severe gastrointestinal disease (e.g. diabetic gastroparesis) and previous medullary thyroid cancer (MTC) or family history of MTC or multiple endocrine neoplasia 2A or 2B. \(^{137}\) (Level II-1)

**Liraglutide**

- Liraglutide is given subcutaneously, once a day at any time of the day but at the same time every day.
- Liraglutide is indicated for use in combination with oral agents and insulin. It resulted in reductions in the mean A1c of 0.8–1.4%. \(^{138-141}\) (Level I)
- There is no increased risk of hypoglycaemia and it may result in weight loss of 3.2 kg. \(^{142}\) (Level I)
- The starting dose is 0.6 mg daily for a week followed by 0.6 mg weekly titration to a maximum dose of 1.8 mg daily. This is to minimise gastrointestinal side effects such as nausea, vomiting and diarrhea. \(^{143}\) (Level I)
- In patients who are on combination of metformin and SU with an A1c <10.0%, the addition of liraglutide produced similar glycaemic improvement compared to insulin glargine without any increase risk of hypoglycaemia and weight gain. \(^{139}\) (Level I)
Lixisenatide
- Lixisenatide is given subcutaneously, once a day at any time of the day but at the same time every day.
- Lixisenatide can be used in combination with OADs and/or basal insulin. Monotherapy with lixisenatide results in A1c reduction of 0.5-0.7%.
- Nausea, vomiting, diarrhoea and headache are common.

Caution:
- GLP-1 RA is not a substitute for insulin.
- GLP-1 RA should not be used in patients with a history of pancreatitis.
- GLP-1 RA should not be used if e-GFR <30 mL/min/1.73 m² (exenatide and lixisenatide) and e-GFR <60 mL/min/1.73 m² (liraglutide).

Table 18: GLP-1 RA Formulations and Dosage

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide IR</td>
<td>5 µg/20 µL</td>
<td>5 µg BD</td>
<td>10 µg BD</td>
</tr>
<tr>
<td></td>
<td>10 µg/40 µL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide XR</td>
<td>2 mg</td>
<td>2 mg weekly</td>
<td>2 mg weekly</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75 mg / 1.5 mg</td>
<td>0.75 mg weekly</td>
<td>1.5 mg weekly</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>6 mg/mL</td>
<td>0.6 mg OD</td>
<td>1.8 mg OD</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>50 µg/mL</td>
<td>10 µg OD</td>
<td>20 µg OD</td>
</tr>
<tr>
<td></td>
<td>100 µg/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- For fixed combination formulations, please refer to specific product inserts.

3.6.3 General Guidelines for Use of Oral Anti-diabetic Agents
- OAD can be used as monotherapy or in combination with other OAD(s), and/or injectable agents (e.g insulin, GLP-1 receptor agonist).
- Agents that are known to improve fasting hyperglycaemia include metformin and TZDs while others reduce mainly postprandial hyperglycaemia.
- As first line therapy, metformin is the preferred choice. Other OAD agents are acceptable alternatives.
- If glycaemic targets are not achieved, intensification of treatment should be made every 3 months.
- If monotherapy fails, combination of other agents is recommended.
- Compliance may be improved with daily dosing OAD agents.
- OAD agents are usually not the first line therapy in stress hyperglycaemia. Insulin therapy is recommended.
- Targets for control should be individualised.
- When indicated, start with a minimal dose of OAD agent, while re-emphasising diet and physical activity. This dose should be optimised gradually.
3.6.4 Combination of OADs, GLP-1 RA and Insulin

If targets have not been reached after optimal OAD therapy, consider adding:
• Pre-bed basal insulin, or
• Pre-dinner premixed insulin, or
• GLP-1 RA, as an alternative to intermediate or long-acting insulin with less incidence of hypoglycaemia and weight gain (provided the A1c is <10.0%)

Combining insulin with the following OADs has been shown to be effective in T2DM:
• Biguanide (metformin) 148-150 (Level I)
• Insulin secretagogue (SU) 151 (Level I)
• Insulin sensitizer (TZD) 152 (Level I) (combination of a TZD and insulin is not generally recommended)
• Alpha-glucosidase inhibitor (AGI) 90,153 (Level I)
• DPP-4 inhibitor 154-156 (Level I)
• SGLT2 inhibitor 116-119 (Level I)
• GLP-1 RA 124,142,144 (Level I)

Insulin dosage should be increased until target FPG is achieved safely. If A1c targets are not achieved despite normal FPG, then postprandial plasma glucose (PPG) should be monitored. If A1c target is not achieved, further insulin intensification is required.

In patients who are on insulin, metformin should be continued indefinitely unless patients develop CKD stage 4 and 5.

Recommendations: Combination of Anti-diabetic Agents

1. OAD can be used as monotherapy or in combination with other OAD(s), and/or injectable agents (e.g insulin, GLP-1 RA). [Grade A]
2. As first line therapy, metformin is the preferred choice. Other OAD agents are acceptable alternatives. [Grade A]
3. If targets are not met after optimal OAD therapy, consider adding GLP-1 RA (if A1c <10.0%) or basal insulin. [Grade A]
4. If glycaemic targets are not achieved, intensification of treatment should be made every 3 months. [Grade C]

3.6.5 Initiation, Optimisation & Intensification of Insulin Therapy
(adapted from Practical Guideline to Insulin Therapy in Type 2 Diabetes Mellitus) 157 (Level III)

T2DM is a progressive disease characterised by worsening glycaemia due to progressive decline in beta cell function. 158 (Level III) This ultimately renders oral agents ineffective and the majority of patients with T2DM will require long-term insulin therapy.

Persistent hyperglycaemia in spite of optimal OAD agents and weight loss suggests beta cell failure. However, it is important to exclude chronic infections, malignancies or medications as a cause of the weight loss.

Insulin therapy is suitable at all stages of T2DM, for all ages, and with a wide range of treatment options and regimens. Insulin can be combined with OADs or GLP-1 receptor agonists (GLP-1 RA).

Insulin therapy should be considered in the following situations:
• Inadequate glycaemic control on optimal dose and number of OADs 159 (Level I) (refer Algorithm 4)
• As a short term use in the following:
  a) Acute illness or surgery
  b) Pregnancy
  c) Breast-feeding
  d) Severe metabolic decompensation (e.g. diabetic ketoacidosis, hyperosmolar hyperglycaemic state)

• As initial therapy in newly diagnosed T2DM
  a) Symptomatic (osmotic symptoms) regardless of A1c or FPG
  b) A1c >10% or FPG >13 mmol/L
  c) As part of early insulinisation treatment regime\textsuperscript{160} (Level I), \textsuperscript{161} (level II-2)

### Insulin Types and Regimens
The insulin currently used in this country are human insulin derived by recombinant technology or insulin analogue (genetically modified human insulin). Both types of insulin are further divided into prandial, basal and premixed according to their pharmacokinetic profiles.

• **Prandial insulin** is administered pre-meal because of its short or rapid onset of action in controlling postprandial glucose excursion. It is also used in insulin pumps.

• **Basal insulin** is administered once or twice daily. The intermediate or long-acting pharmacokinetic profile covers the basal insulin requirements in between meals and night time.

• **Premixed insulin** is biphasic insulin that incorporates both the short or rapid-acting insulin with intermediate-acting insulin into a single preparation to cover for both postprandial glucose excursion as well as basal insulin needs
Table 19: Types of insulin and Their Pharmacokinetics Profiles

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset of Action</th>
<th>Peak Action (hours)</th>
<th>Duration of Action (hours)</th>
<th>Timing of Administration of Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Acting, Regular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actrapid</td>
<td>30–60 min</td>
<td>2–4</td>
<td>6–10</td>
<td>30 min before meal</td>
</tr>
<tr>
<td>Humulin R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insuman R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insugen R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid Analogue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart (Novorapid)</td>
<td>0–20 min</td>
<td>1–3</td>
<td>3–5</td>
<td>5–15 min before or immediately after meals</td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting, NPH</td>
<td>1–2 hour</td>
<td>4–8</td>
<td>8–12</td>
<td>Pre-breakfast / Pre-bed</td>
</tr>
<tr>
<td>Insulatard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insuman N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insugen N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Acting Analogue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>30–60 min</td>
<td>Less peak</td>
<td>16–24</td>
<td>Same time everyday</td>
</tr>
<tr>
<td>Detemir</td>
<td>30–60 min</td>
<td>Less peak</td>
<td>16–24</td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td>30–90 min</td>
<td>Less peak</td>
<td>24–40</td>
<td></td>
</tr>
<tr>
<td>Premixed Insulins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixtard 30</td>
<td>30 min</td>
<td>dual</td>
<td>18–23</td>
<td>30–60 min before meals</td>
</tr>
<tr>
<td>Humulin 30/70</td>
<td>30 min</td>
<td>dual</td>
<td>16–18</td>
<td></td>
</tr>
<tr>
<td>Novomix 30</td>
<td>10–20 min</td>
<td>1–4</td>
<td>16–20</td>
<td>5–15 min before meals</td>
</tr>
<tr>
<td>Humalog mix 25/75</td>
<td>15 min</td>
<td>0.5–2.5</td>
<td>16–18</td>
<td></td>
</tr>
<tr>
<td>Humalog mix 50/50</td>
<td>15 min</td>
<td>0.5–2.5</td>
<td>16–18</td>
<td></td>
</tr>
<tr>
<td>IDegAsp 30</td>
<td>10–20 min</td>
<td>1–4</td>
<td>24–40</td>
<td>5–15 min before meals</td>
</tr>
</tbody>
</table>

The time course of action may vary in different individuals, or at different times in the same individual. The variations and time periods indicated above should be considered as general guidelines only. The higher the dose of the insulin, the longer is the duration of action.

The long acting insulin analogue, which has less peak, results in lower hypoglycaemic episodes and reduced weight gain compared to conventional insulin. At higher doses the long acting insulin analogue may have a significant peak. The rapid acting insulin analogues can be administered immediately before meals. Based on Cochrane reviews, insulin analogues are not superior to conventional human insulin in terms of efficacy other than reduced risk of symptomatic nocturnal hypoglycaemic events.
Insulin Regimen

An ideal insulin regimen should mimic the physiological insulin response to meals and endogenous hepatic glucose production. The choice of insulin regimen should be individualised, based on the patient’s glycaemic profile, dietary pattern and lifestyle.

Basal bolus therapy using the combination of basal and prandial insulin offers the most physiological insulin action.

Insulin initiation can be done safely in an outpatient setting. At initiation, the insulin dose prescribed is usually low to avoid hypoglycaemia. All patients prescribed insulin therapy should be advised to perform self-monitoring of blood glucose (SMBG) and empowered to self-adjust their insulin doses.

Insulin dose optimisation requires gradual, safe and prompt titration of insulin dose according to SMBG. The insulin dose should be adjusted at least weekly to achieve glycaemic targets. Optimisation of the insulin dose should be an interactive process between the healthcare provider and the patient. This can be done at the diabetic resource centre, via telephone calls or text messages. It should be done within the first 3 months of starting insulin.

Often the insulin regimens started may need modification, which require switching to more intensive insulin regimens for better glycaemic control. This may entail increased number of injections.

Insulin pump may be considered in patients who are still not controlled while on basal-bolus regime.

Barriers to effective insulin therapy:

- There are numerous barriers to effective insulin therapy. These include patients and healthcare providers’ factors.
- The biggest barrier is compliance and this should be adequately ascertained prior to any effort to intensify insulin therapy.
Algorithm 4: Initiation and Optimisation of Insulin Therapy

Newly diagnosed DM & T2DM
- Symptomatic (osmotic symptoms) regardless A1c or FBS
- A1c >10% or FPG >13 mmol/L
- T2DM on maximal OADs
  - A1c >7%

Glycaemic abnormality?
FPG, SMBG

Normal Fasting
High daytime BG
Start PRANDIAL only
(usually TDS premeals)
Optimise dose
Start BASAL only
(bedtime)
Optimise dose
Start PREMIXED OD
(pre-dinner)
Optimise dose
Start PREMIXED BD
(prebreakfast & predinner)
Optimise dose
Start BASAL BOLUS
(premeals, bedtime)
Optimise dose
Sequential addition of prandial insulin
Add 3 prandial insulin
Add basal insulin

BASAL PLUS
(pre-meals and bedtime)
Optimise dose
PREMIXED TDS
(pre-meals),
Optimise dose
PREMIXED BD PLUS PRANDIAL
(pre-lunch),
Optimise dose
BASAL BOLUS (prandial insulin at pre-meals, basal insulin at bedtime) Optimise dose

Note:
1. Metformin should be continued while on insulin therapy unless contraindicated or intolerant
2. Sulphonylureas/Meglitinides should be withdrawn once prandial insulin is used regularly with meals
3. Insulin dose should be optimised prior to switching/intensifying regimens
Table 20: Insulin Regimen

<table>
<thead>
<tr>
<th>No of injections per day</th>
<th>Insulin regimen</th>
<th>Type of insulin and timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BASAL</td>
<td>Intermediate acting (NPH) insulin pre-bed</td>
</tr>
<tr>
<td></td>
<td>BASAL</td>
<td>Long-acting analogue once daily</td>
</tr>
<tr>
<td></td>
<td>PREMIXED OD</td>
<td>Premixed/premixed analogue pre-dinner</td>
</tr>
<tr>
<td>2</td>
<td>BASAL</td>
<td>Intermediate acting (NPH) pre-breakfast and pre-dinner</td>
</tr>
<tr>
<td></td>
<td>PREMIXED BD</td>
<td>Premixed insulin pre-breakfast and pre-dinner</td>
</tr>
<tr>
<td></td>
<td>BASAL-PLUS 1</td>
<td>Basal insulin once daily + 1 prandial insulin</td>
</tr>
<tr>
<td>3</td>
<td>BASAL-PLUS 2</td>
<td>Basal insulin once daily + 2 prandial insulin</td>
</tr>
<tr>
<td></td>
<td>PRANDIAL</td>
<td>Prandial insulin pre-breakfast, pre-lunch and pre-dinner</td>
</tr>
<tr>
<td></td>
<td>PREMIXED TDS</td>
<td>Premixed pre-breakfast, pre-lunch and pre-dinner</td>
</tr>
<tr>
<td></td>
<td>PREMIXED-PLUS 1</td>
<td>Premixed insulin pre-breakfast and pre-dinner + 1 prandial insulin pre-lunch</td>
</tr>
<tr>
<td></td>
<td>PREMIXED-PLUS 2</td>
<td>Prandial insulin pre-breakfast and pre-lunch + premixed insulin pre-dinner</td>
</tr>
<tr>
<td>4</td>
<td>BASAL-BOLUS 1</td>
<td>Basal insulin once daily + prandial insulin pre-breakfast, pre-lunch and pre-dinner</td>
</tr>
<tr>
<td>5</td>
<td>BASAL-BOLUS 2</td>
<td>Intermediate acting (NPH) insulin pre-breakfast and pre-dinner + prandial insulin pre-breakfast, pre-lunch and pre-dinner</td>
</tr>
</tbody>
</table>

General Guidelines for Long Term Use of Insulin

- The basal intermediate acting insulin should be administered pre-bed (preferably not earlier than 10 p.m.) because of the risk of hypoglycaemia in the early hours of the morning if given earlier.
- It is not necessary to have an extra meal or snack after intermediate or long acting insulin.
- Requirements of high dose of insulin (>1.5 unit/kg per day) should prompt a search for an underlying cause/secondary problems such as non-compliance, incorrect dosing or timing of injection, hypertrophy of injection sites, inter meal hypoglycaemia with rebound hyperglycaemia, expired insulin or expired strips and occult infections.
- There is no maximum dose of insulin that can be injected.
- The rate of absorption from the injections depends on the site. Patients should be encouraged to rotate all their injection sites in the abdomen.
- Assessment of pancreatic reserve (e.g. glucagon stimulation test, insulin/C-peptide estimations) prior to insulin use is unnecessary in clinical practice.

Insulin Pump

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is another method to deliver insulin to diabetes patients. Insulin pump therapy is intended to closely mimic normal physiological insulin profile. Insulin pump therapy utilises only fast acting insulin and eliminates the use of long-acting insulin. It is safe and effective and can be initiated at any age. A Cochrane review showed that insulin pump (without glucose sensor) gave slightly improved metabolic control over basal-bolus therapy. In general, the combination of insulin pump and continuous glucose sensor resulted in improved control and less hypoglycaemia over basal bolus therapy alone.
• **Indication for Insulin Pump Therapy:**
  a) Inadequate glycaemic control with MDI (multiple daily injections) therapy
  b) Recurrent severe hypoglycaemia
  c) Hypoglycaemia unawareness
  d) Dawn phenomenon
  e) Gastroparesis
  f) Frequent diabetic ketoacidosis

• **Patient’s Pre-requisite for Insulin Pump Therapy**
  a) Patient is motivated with a strong desire to improve his/her health.
  b) Demonstrates independent diabetes self-management.
  c) Able to practice carbohydrate counting and understanding of basic insulin action.
  d) Demonstrates emotional stability, able to attend education sessions and clinic appointments.

**Recommendations: Insulin Initiation, Optimisation and Intensification**

1. The choice of insulin regimen should be individualised, based on the patient’s glycaemic profile, dietary pattern and lifestyle. *[Grade C]*
2. The biggest barrier is compliance and this should be adequately ascertained prior to any effort to intensify insulin therapy. *[Grade C]*
3. Optimisation of insulin therapy should be done within the first 3 months of insulin initiation. *[Grade C]*
3.7.1 Algorithm 5: Treatment Algorithm for Newly Diagnosed T2DM

**Note:** Please note that the diagnosis of diabetes begins at A1c ≥6.3% (based on the MSSM study), while the A1c target for treatment is ≤6.5% (based on the ADVANCE study).

**Footnote:** The agents above are based on historical order:

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Effectiveness</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Efficacious, low risk of hypoglycaemia and weight neutral</td>
<td>GLP-1 RA, SGLT-2</td>
</tr>
<tr>
<td>SU, Glimes, Insulin</td>
<td>Efficacious, risk of hypoglycaemia and weight gain</td>
<td>T2D</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Moderate efficacy, low risk of hypoglycaemia and weight neutral</td>
<td>AGI</td>
</tr>
</tbody>
</table>
### Table 21: Treatment Recommendations for Patients on Clinic Follow-up

<table>
<thead>
<tr>
<th>Glycaemic Control</th>
<th>A1c 6.5–&lt;7.5% or FPG 6–&lt;8 mmol/L</th>
<th>A1c 7.5–&lt;8.5% or FPG 8–&lt;10 mmol/L</th>
<th>A1c 8.5–10.0% or FPG 10–13 mmol/L</th>
<th>A1c &gt;10.0% or FPG &gt;13 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle Treatment</strong></td>
<td>Start metformin (if metformin not tolerated, use an agent from Box 1)</td>
<td>Start metformin and another agent from Box 1 (dual therapy)</td>
<td>Start metformin and 2 other agents from Box 1 (triple therapy)</td>
<td>Start metformin &amp; another agent + insulin (basal or premixed od)</td>
</tr>
<tr>
<td><strong>Monotherapy (Metformin preferred)</strong></td>
<td>Add 1 agent from Box 1 (dual therapy)</td>
<td>Add 2 agents from Box 1 (triple therapy)</td>
<td>Add 2 agents from Box 1 + insulin (basal or premixed od)</td>
<td>Initiate &amp; intensify§ insulin (MDI) and continue metformin</td>
</tr>
<tr>
<td><strong>Dual Therapy</strong></td>
<td>Add 1 agent from Box 1 (triple therapy)</td>
<td>Add 1 agent from Box 1 or insulin (basal or premixed od)</td>
<td>Add 1 agent from Box 1 + insulin (basal or premixed od)</td>
<td>Initiate &amp; intensify§ insulin (MDI) and continue dual therapy (except SU/glinides)</td>
</tr>
<tr>
<td><strong>Triple Therapy</strong></td>
<td>Add 1 agent from Box 1 (quadruple therapy)</td>
<td>Add 1 agent from Box 1 or insulin (basal or premixed od)</td>
<td>Add insulin (basal or premixed od) and continue triple therapy</td>
<td>Initiate &amp; intensify§ insulin (MDI) and continue triple therapy (except SU/glinides)</td>
</tr>
</tbody>
</table>

MDI = Multiple daily injections; § Intensify involves changing the regimen; SU = sulphonylureas

### Box 1: Selection of Anti-diabetic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU</td>
<td>Efficacious</td>
<td>Risk of hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Efficacious</td>
<td>Risk of hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>AGI</td>
<td>Modest efficacy</td>
<td>Low risk of hypoglycaemia, weight neutral</td>
</tr>
<tr>
<td>TZD</td>
<td>Efficacious</td>
<td>Low risk of hypoglycaemia, weight gain</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Moderate efficacy</td>
<td>Low risk of hypoglycaemia, weight neutral</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Moderate efficacy</td>
<td>Low risk of hypoglycaemia, weight loss</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>Moderate efficacy</td>
<td>Low risk of hypoglycaemia, weight loss</td>
</tr>
</tbody>
</table>

**Note:**
1. If symptomatic (weight loss, polyuria, etc) at any A1c and FPG level, consider insulin therapy.
2. Glycaemic target should be individualised, however try to achieve as near normal glycaemia as possible without causing hypoglycaemia.
3.7.3 Algorithm 6: Suggested Treatment Approach for Specific Patient Profiles

2\textsuperscript{nd} Gen SU = selected 2\textsuperscript{nd} generation sulphonylurea (gliclazide); DPP-4i = dipeptidyl peptidase-4 inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitor; GLP-1 RA = glucagon-like peptide 1 receptor agonist. DPP-4i should be stopped once GLP-1 RA is introduced.

\textbf{Note}:
1. Patients who are well-controlled on their existing drugs should continue with the treatment regime.
2. Bariatric surgery may be considered in patients with BMI \( \geq 32 \text{ kg/m}^2 \) and their diabetes cannot be controlled by lifestyle changes and pharmacotherapy.
### 3.7.4 Table 22: Efficacy of Various Anti-diabetic Agents

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>SU</th>
<th>GLN</th>
<th>AGI</th>
<th>TZD</th>
<th>DPP4-i</th>
<th>SGLT2-i</th>
<th>GLP-1 RA</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c reduction, %</td>
<td>1.0-1.5</td>
<td>0.4-1.6</td>
<td>1.0-1.2</td>
<td>0.5-0.8</td>
<td>0.5-1.4</td>
<td>0.5-0.8</td>
<td>0.2-0.8</td>
<td>0.5-1.4</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>FPG vs PPG</td>
<td>FPG</td>
<td>FPG</td>
<td>Both</td>
<td>PPG</td>
<td>FPG</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↑↑</td>
</tr>
<tr>
<td>Weight change</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↓?</td>
<td>←</td>
</tr>
<tr>
<td>Bone loss</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↑</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>CKD</td>
<td>Avoid if GFR&lt;30</td>
<td>Hypoglycaemia</td>
<td>Hypoglycaemia</td>
<td>←</td>
<td>Fluid retention</td>
<td>Dose adjustment</td>
<td>Avoid if GFR&lt;60</td>
<td>Avoid if GFR&lt;30</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>References</td>
<td>77 (Level I)</td>
<td>168,169 (Level I)</td>
<td>85 (Level I)</td>
<td>170 (Level I)</td>
<td>88-92 (Level I)</td>
<td>151-153 (Level I)</td>
<td>113-116 (Level I)</td>
<td>121 (Level I)</td>
<td>160,161,171, 172 (Level I)</td>
</tr>
</tbody>
</table>

MET = metformin; SU = sulphonylureas; GLN = glinides; GLP-1 RA = glucagon-like peptide-1 receptor agonists; DPP4-i = dipeptidyl peptidase-4 inhibitors; SGLT2-i = sodium-glucose co-transporter 2 inhibitors; AGI = α-glucosidase inhibitor; TZD = thiazolidinediones

The efficacy data for the above anti-diabetic agents were established with baseline A1c level below 10%. Efficacy of all OADs is dependent on the baseline A1c levels. The higher the A1c level, the more efficacious is the agent.
3.8 Monitoring

3.8.1 Glycated Haemoglobin (A1c)
Perform A1c approximately every 3–6 months (intervals depend on whether A1c targets are achieved):
• 3 monthly, if A1c is above target and to allow assessment of effect of therapeutic adjustment.
• 6 monthly, if A1c target is achieved and stable.

A1c has a strong predictive value for diabetes complications. Reduction in A1c will result in a reduction in risk of microvascular complications in the immediate short-term \(^{171}\) (Level I) and macrovascular complications in the long-term. \(^{171,172}\) (Level I)

A1c target should be individualised. Therapy in most patients with T2DM should be targeted to achieve A1c \(\leq 6.5\%\). The more aggressive target should be attempted in those with long life-expectancy, no comorbidities and these targets can be achieved without causing severe hypoglycaemia.

Use of point-of-care testing for A1c provides the opportunity for timely treatment changes in outpatient clinic settings.

Limitations of A1c
A1c utility is limited in situations with haemolysis (increased RBC turnover), e.g. haemoglobinopathy and anaemia where A1c results do not correlate with glucose levels. In these situations, A1c is not recommended, and alternatives such as SMBG should be considered. In addition, A1c does not provide information on glucose variability and does not capture hypoglycaemia. In such circumstances, a combination of SMBG and A1c is appropriate.

Figure 1: Correlation Between A1C Levels and Mean Glucose Levels \(^{173}\) (Level II-2)
Table 23: Mean Glucose Levels for Specified A1c Levels

<table>
<thead>
<tr>
<th>A1c (%)</th>
<th>Plasma Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>&lt;6.5</td>
<td>7.0</td>
</tr>
<tr>
<td>&lt;7.0</td>
<td>8.6</td>
</tr>
<tr>
<td>&lt;7.5</td>
<td>-</td>
</tr>
<tr>
<td>&lt;8.0</td>
<td>10.2</td>
</tr>
<tr>
<td>9.0</td>
<td>11.8</td>
</tr>
<tr>
<td>10.0</td>
<td>13.4</td>
</tr>
<tr>
<td>11.0</td>
<td>14.9</td>
</tr>
<tr>
<td>12.0</td>
<td>16.5</td>
</tr>
</tbody>
</table>

- The above table shows the correlation between A1c and mean glucose levels based on ADAG and CGM studies. 174 (Level II-1)

3.8.2 Fructosamine
The evidence that correlates fructosamine to average glucose levels and its prognostic significance are not as strong as A1c. 175 (Level III)

3.8.3 Self-Monitoring of Blood Glucose (SMBG)
Self-monitoring of blood glucose (SMBG) is the method of choice in assessing glycaemic control and prevent hypoglycaemia. As part of an educational initiative, SMBG should be recommended in patients on insulin and is desirable for those on OAD agents. 4 (Level III)

Frequency of blood glucose testing depends on the glucose status, glucose goals and mode of treatment. Although SMBG has not been shown to have a significant impact on outcome measures such as A1c and body weight, it is recommended as part of a wider educational strategy to promote self-care.

Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve pre-defined goals. The need for and frequency of SMBG should be re-evaluated at follow-up visits.

Continuous glucose monitoring (CGM) is becoming a useful option, especially for patients with T1DM, those on intensive insulin regimens to improve glycaemic control, individuals with nocturnal hypoglycaemia and hypoglycaemia unawareness.

Table 24: Recommendations for Self-Monitoring of Blood Glucose

<table>
<thead>
<tr>
<th>Mode of Treatment</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Diet only</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>OADs</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Insulin</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>
Glucose Monitoring in Relation to Different Insulin Regime

Once pre-meal glucose levels are achieved, PPG testing is recommended for fine-tuning of insulin dose. This information will allow adjustments of insulin dosage after taking into account the effect of diet and physical activity.

OAD(s) + Bedtime Insulin

- Values before breakfast give information about bedtime insulin (Refer to Figure 2) or once daily basal long-acting insulin (Refer to Figure 3)

Basal-Bolus Insulin Regimen

- Values before breakfast give information about pre-dinner or pre-bed intermediate acting insulin.
- Values before other main meals (pre-lunch or pre-dinner) reflect short acting insulin taken at the previous meal.
- Values at pre-bed give information about short acting insulin given before dinner.
Twice Daily Premixed or Combination Intermediate-Acting with Short-Acting Insulin

Breakfast       Lunch       Dinner       Bedtime

Figure 5: Intermediate-Acting with Short-Acting Insulin

- Values before breakfast give information about pre-dinner or pre-bed intermediate or long acting insulin
- Values at pre-lunch give information about short acting insulin given before breakfast
- Values at pre-dinner give information about the intermediate acting insulin given before breakfast
- Values at pre-bed give information about short acting insulin given before dinner
- Ideally these tests should be done on a daily basis or if possible at least one 24-hour cycle per week.

▲ = Recommended timing of SMBG
3.8.4 Monitoring of Other Risk Factors

- Monitoring of glycaemic control, comorbidities, complications and other CVD risk factors should follow the following schedule (Table 25):

Table 25: Clinical Monitoring Schedule

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial Visit</th>
<th>3-monthly visit</th>
<th>Annual visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>BMI</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Eye: Visual acuity</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Fundoscopy</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Feet: Pulses</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Dental Check-up</td>
<td>√</td>
<td>√ (6-monthly)</td>
<td>√</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>A1c</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>√</td>
<td>+</td>
<td>√</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>√</td>
<td>+</td>
<td>√</td>
</tr>
<tr>
<td>Creatinine/BUSE</td>
<td>√</td>
<td>+</td>
<td>√</td>
</tr>
<tr>
<td>Liver function test</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Urine microscopy</td>
<td>√</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Albuminuria*</td>
<td>√</td>
<td>+</td>
<td>√</td>
</tr>
<tr>
<td>ECG**</td>
<td>√</td>
<td>+</td>
<td>√</td>
</tr>
</tbody>
</table>

* Microalbuminuria if resources are available; ** At initial visit and if symptomatic.

- Modified from Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation (IDF) Western Pacific Region: Type 2 Diabetes Practical Targets and Treatments, 2005. [176 (Level III)]

Recommendations: Monitoring

1. Glycaemic targets must be individualised. Therapy in most patients with T2DM should be targeted to achieve an A1c ≤6.5%, if achievable without significant hypoglycaemia. Reduction in A1c has been shown to decrease the risk of microvascular [Grade A] and macrovascular complications. [Grade C]
2. To achieve an A1c ≤6.5%, aim for FPG or pre-prandial plasma glucose targets of 4.4–7.0 mmol/L and 2-hour PPG targets of 4.4–8.5 mmol/L. [Grade B]
3. SMBG should be recommended in patients on insulin and is desirable for those on OAD agents. [Grade C]
4. Monitoring of glycaemic control, comorbidities, complications and other CVD risk factors should also be done at initial visit and whenever indicated subsequently. [Grade C]
3.9 Management of Comorbidities in Type 2 Diabetes Mellitus

3.9.1 Hypertension and Diabetes

- Hypertension is a common comorbidity of diabetes, with a prevalence of 70.1% among patients who are followed up with National Diabetes Registry. ² (Level II-3)

- Hypertension should be detected and treated early in the course of T2DM to prevent cardiovascular disease (CVD) and to delay the progression of renal disease and diabetic retinopathy.

- Pharmacological treatment should be initiated in patients with diabetes when the blood pressure (BP) is persistently >140 mm Hg systolic and/or >90 mm Hg diastolic ¹⁷⁷ (Level I) and treat to goal systolic (SBP) of lower than 135 mm Hg and diastolic (DBP) lower than 75 mm Hg. ⁴¹ (Level I)

- Randomised clinical trials have demonstrated reduction of coronary heart disease (CHD) events, stroke and nephropathy when lowering SBP to <140 mm Hg. ²⁶ (Level I), ¹⁷⁸ (Level II-3) The BP lowering arm of the ADVANCE trial (with a final BP of 135/75 mm Hg) showed a significant 9%, 14% and 18% reduction in the relative risk of major macro- and microvascular complications, total coronary events and cardiovascular deaths, respectively, contributing to 14% reduction in total mortality. ⁴¹, ⁴² (Level I)

**Management**

- Non-pharmacological management cannot be over emphasised. Dietary counseling should target at optimal body weight and dietary sodium restriction is advisable. Further sodium restriction, with or without a diuretic, may be necessary in the presence of nephropathy or when the BP is difficult to control. ⁴¹ (Level I)

- Pharmacological treatment for patients with diabetes and hypertension should comprise a regimen that includes either an ACEI or an ARB as first line. ACEIs have been regarded as drug of choice based on extensive data. ¹⁷⁹, ¹⁸⁰ (Level I) If an ACEI is not tolerated, an ARB should be considered. ¹⁸¹ (Level I) ARBs have been reported to be superior to conventional non-ACE-inhibitors antihypertensive drugs in terms of slowing the progression of nephropathy at the microalbuminuric and overt nephropathy stages. ¹⁸¹-¹⁸⁴ (Level I)

- Multiple drug therapy is generally required to achieve blood pressure targets. 90% of patients require three antihypertensive medications to achieve target. ⁶⁸ (Level I) Diuretics, calcium channel blockers (CCBs), beta-blockers and peripheral alpha-blockers may be used as add-on therapy.

- It is recommended that one or two antihypertensive medications should be administered at bedtime. There is evidence that taking at least one antihypertensive medication at bedtime reduce risk of CVD events. ¹⁸⁵ (Level I)
Table 26: Choice of Antihypertensive Drugs in Diabetic Patients with Concomitant Conditions

<table>
<thead>
<tr>
<th>Concomitant Disease</th>
<th>Diuretics</th>
<th>Beta-blockers</th>
<th>ACEIs</th>
<th>CCBs</th>
<th>Peripheral alpha-blockers</th>
<th>ARBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (without nephropathy)</td>
<td>+</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>DM (with nephropathy)</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
<td>+++^</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Gout</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+++</td>
<td>+++#</td>
<td>+++</td>
<td>+@</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Asthma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Non-diabetic renal impairment</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+^</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>+</td>
<td>+</td>
<td>+++$</td>
<td>+</td>
<td>+</td>
<td>++$</td>
</tr>
<tr>
<td>Elderly with no co-morbid conditions</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

ACEIs = angiotensin-converting enzyme inhibitors; CCBs = calcium-channel blockers; ARBs = angiotensin receptor blockers; DM = diabetes mellitus

- Adapted from the Malaysian Clinical Practice Guidelines for the Management of Hypertension, 2013. 186 (Level III)
- The grading of recommendation from (+) to (+++) is based on increasing levels of evidence and/or current widely accepted practice.

+/-: Use with care
- Contraindicated
^ Only non-dihydropyridine CCB
# Metoprolol, bisoprolol, carvedilol – dose needs to be gradually titrated
@ Current evidence available for amlodipine and felodipine only
$ Contraindicated in bilateral renal artery stenosis

- In pregnant patients with diabetes and chronic hypertension, blood pressure target goals of 110-129/65-79 mm Hg are suggested, taking into account the long-term maternal health and minimising impaired fetal growth. ACEIs and ARBs are contraindicated during pregnancy.

- Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, nifedipine, diltiazem and prazosin. 187 (Level III)
3.9.2 Hyperlipidaemia and Diabetes

DM is a coronary heart disease (CHD) risk equivalent. Control of hyperglycaemia in T2DM has not been associated with significant decrease in CVD events except in overweight people with diabetes who were given metformin. Thus, efforts must also be directed to control other risk factors such as dyslipidaemia, hypertension and other new emerging risk factors.

Screening

In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL cholesterol <2.6 mmol/L, HDL cholesterol >1.0 mmol/L in males and >1.2 mmol/L in females and TG <1.7 mmol/L), lipid assessments may be repeated every year.

Primary target: LDL cholesterol

- In individuals without overt CVD
  - All patients over the age of 40 should be treated with a statin regardless of baseline LDL cholesterol levels.  
  - The target of LDL cholesterol level is 2.6 mmol/L.
  - If the above target is unattainable, aim for a 50% reduction in pre-treatment LDL-C level.

- In individuals with overt CVD
  - All patients should be treated with a statin.
  - The target of LDL cholesterol level is 1.8 mmol/L.
  - If the above target is unattainable, aim for a 50% reduction in pre-treatment LDL-C level.

Secondary target: Non-HDL cholesterol, HDL cholesterol and TG

- Non-HDL cholesterol <3.4 mmol/L (when TG >4.5 mmol/L)
- HDL cholesterol >1.0 mmol/L for males, >1.2 mmol/L for females
- TG <1.7 mmol/L

In adolescents with T2DM, screening for lipid disorders should be done at diagnosis after glycaemic control is achieved. If normal lipid values are obtained, screening should be repeated every 2 years.

Management

- Lifestyle modification focusing on the reduction of saturated fat, trans fat, and cholesterol intake; weight loss (if indicated) and increased physical activity have been shown to improve the lipid profile in patients with diabetes.
- Lowering LDL is the main aim of treatment.
Any effort to increase HDL should be done together with the main purpose to reduce LDL. Using pharmacotherapy to increase HDL alone showed mixed result, with no or small benefit. 199 (Level III)

In patients with very high TG, improving diabetes control and reduction of carbohydrate intake is emphasised.

Lowering TG in patients with clinical CVD and normal LDL cholesterol level with a fibrate is associated with mixed results in CVD outcomes;200-203 (Level I) modest improvement in the FIELD study 204 (Level I) but no improvement in the ACCORD study. 205 (Level I)

Nicotinic acid should only be used in patients with high risk of pancreatitis with a TG level of more than 10 mmol/L in those who does not respond adequately to fibrates. 206-208 (Level I)

In patients with high TG >4.5 mmol/L, when LDL cannot be calculated, non-HDL level is a target of therapy and can be calculated from a non-fasting serum.

Combination therapy using simvastatin and ezetimibe has helped to achieve lipid targets more than simvastatin alone. 209 (Level I)

Statin therapy is contraindicated in pregnancy.

Lipid lowering medications should only be initiated in those >10 years old. 195 (Level III)

Monitoring of lipid levels should be performed every three months during intensification of lipid therapy.

Table 27: Drug Therapy for Diabetic Dyslipidaemia

<table>
<thead>
<tr>
<th>Lipid Goal</th>
<th>Initial Drug</th>
<th>Suggested Addition in Order of Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lower LDL cholesterol</td>
<td>Statins</td>
<td>Ezetimibe 209 (Level I)</td>
</tr>
<tr>
<td>2. Increase HDL cholesterol</td>
<td>Fibrates 205,210 (Level I)</td>
<td>Statins**</td>
</tr>
<tr>
<td>3. Lower TG</td>
<td>Fibrates or Nicotinic acid* 205 (Level I)</td>
<td>Fibrates 200-203 (Level I)</td>
</tr>
<tr>
<td>4. Treat combined hyperlipidaemia</td>
<td>Statins**</td>
<td>Resin plus Fibrates Nicotinic Acid 211 (Level I)</td>
</tr>
</tbody>
</table>

* With careful monitoring and keeping dose <1.5 g/day
** High dose may be required

Recommendations: Diabetic Dyslipidaemia

1. All patients without overt CVD over the age of 40 should be treated with a statin regardless of baseline LDL-cholesterol levels. [Grade A]
2. All patients with overt CVD should be treated with a statin. [Grade A]
3.9.3 Obesity and Diabetes

Based on the NDR report 2012, 83.4% of patients are either overweight or obese. Many antidiabetic agents are associated with weight gain, and attempts should be made to minimise these medications without compromising glycaemic control or to switch to alternative agents not associated with weight gain. Table 28 showed the anti-diabetic agents and their effects on weight.

Table 28: Anti-diabetic Agents and Their Effects on Weight

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Metformin</td>
<td>GLP-1 RA</td>
</tr>
<tr>
<td>TZDs</td>
<td>AGI</td>
<td>SGLT2 Inhibitors</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>DPP-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TZD = thiazolidinediones; AGI = alpha-glucosidase inhibitors; DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide 1 receptor agonists; SGLT2 inhibitors = sodium-glucose cotransporter 2 inhibitors

Table 29: Classification of Weight by BMI

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Risk of co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Low (but increased risk of other clinical problems)</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.5-22.9</td>
<td>Optimal</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥23.0</td>
<td></td>
</tr>
<tr>
<td>• Pre-obese</td>
<td>23.0 – 27.4</td>
<td>Increased</td>
</tr>
<tr>
<td>• Obese I</td>
<td>27.5-34.9</td>
<td>High</td>
</tr>
<tr>
<td>• Obese II</td>
<td>35.0-39.9</td>
<td>Very High</td>
</tr>
<tr>
<td>• Obese III</td>
<td>≥40.0</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

Treatment of Overweight and Obesity

- The initial assessment of people with diabetes should include height, weight, BMI (kg/m²) and waist circumference.
- Weight loss of between 5-10% will improve glycaemic control, blood pressure, lipid profile and quality of life.
- The goals of therapy are to achieve optimal glycaemic and metabolic control, through lifestyle modifications including behavioural change, physical activity and dietary interventions.

Non-pharmacological interventions

- Dietary interventions (caloric restriction of 1200 to 1500 kcal/day). Increased physical activity consisting of approximately 250 to 300 minutes per week of moderate-intensity exercise. This includes muscle strengthening and resistance exercises 2 to 3 times per week.

Pharmacological Interventions

- Pharmacotherapy can be considered for diabetic patients with BMI ≥27.0 kg/m² after failing of 6 months of lifestyle modification.
- Two anti-obesity agents have been approved, phentermine and orlistat for the management of obesity. Phentermine is only indicated for short-term use and caution should be exercised in those with poorly-controlled blood pressure and coronary artery disease.
GLP-1 RA when used as anti-diabetic agents is associated with significant weight loss (4.5 kg). (Level I)

Table 30: Anti-obesity Agents Indicated for Use in Diabetes (Level I)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Recommended Duration</th>
<th>Net Weight Loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duromine (Phentermine)</td>
<td>Sympatho-mimetic amine</td>
<td>Appetite suppression</td>
<td>3 months (can be used cyclically)</td>
<td>3.6</td>
</tr>
<tr>
<td>Topiramate + Phentermine</td>
<td>Anticonvulsant/ Sympatho-mimetic amine</td>
<td>Appetite suppression, altered satiety action</td>
<td>56 weeks</td>
<td>8.8</td>
</tr>
<tr>
<td>Xenical</td>
<td>Lipase Inhibitor</td>
<td>Reduced gastrointestinal fat absorption</td>
<td>4 years</td>
<td>6.9</td>
</tr>
<tr>
<td>Locaserin</td>
<td>Serotonin 5 HT2C RA</td>
<td>Appetite suppression</td>
<td>52 weeks</td>
<td>4.8</td>
</tr>
<tr>
<td>Bupropion/ Naltrexone</td>
<td>Antidepressant/opiod RA</td>
<td>Appetite suppression, altered satiety action</td>
<td>48 weeks</td>
<td>6.2</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 RA</td>
<td>Slows gastric motility, reduced satiety</td>
<td>20 weeks</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56 weeks</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Note:
Some of the above agents are yet to be made available in Malaysia, however it is felt that they merit a brief mention.

Bariatric Surgery
- Bariatric surgery is recommended when lifestyle and pharmacological intervention have failed in the severely obese diabetic patients. (Level III)
- The Asian Consensus Meeting on Metabolic Surgery (ACMOMS) recommends bariatric surgery for the following:
  a) Diabetic patients >32 kg/m²
  b) Diabetic patients >30 kg/m² with 1 or more features of metabolic syndrome
- Evaluation should be performed by a multidisciplinary team consisting of endocrinologist, bariatric surgeon, psychiatrist, dietitian and physiotherapist prior to surgery.
- Criteria for bariatric surgery are shown in Table 31:
Table 31: Criteria for Bariatric Surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss history</td>
<td>Failure of previous attempts at weight reduction, including programs such as weight watchers etc.</td>
</tr>
<tr>
<td>Commitment</td>
<td>Expectation that patient will adhere to postoperative care consisting of:</td>
</tr>
<tr>
<td></td>
<td>• Follow up visits with health care team</td>
</tr>
<tr>
<td></td>
<td>• Compliance to medical management</td>
</tr>
<tr>
<td></td>
<td>• Continued dietary restriction</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>± BMI &lt;30 kg/m²</td>
</tr>
<tr>
<td></td>
<td>• Current drug or alcohol abuse</td>
</tr>
<tr>
<td></td>
<td>• Severe psychiatric illness</td>
</tr>
<tr>
<td></td>
<td>• Lack of comprehension of the benefits, risks, expected outcomes and required lifestyle changes.</td>
</tr>
</tbody>
</table>

**Choice of Procedures**

- Bariatric surgery procedures can be classified as restrictive or malabsorptive or combined restrictive and malabsorptive. The most commonly performed surgical procedures for reversing/improving diabetes are roux-en-Y gastric bypass and sleeve gastrectomy. Laparoscopic adjustable gastric banding (LAGB) has been demonstrated to have intermediate success. [219,220 (Level I)]

- Following bariatric surgery, mean excess weight loss is about 55.9% to 61% depending on the surgical procedures. [220,221 (Level I)] In addition there is improvement of the following: [220-222 (Level I)]
  a) T2DM: 78.1% to 92% (often occurring soon after surgery)
  b) Hypertension: 70% to 75%
  c) Dyslipidaemia: 61.7% to 76%

Risks of complications, reoperation and death post-bariatric surgery is small but do exist. It is dependent on the surgeon’s surgical volume and expertise. [222 (Level I)]

**Recommendations: Obesity and Diabetes**

1. In overweight or obese diabetic patients, a structured program of lifestyle modification that includes moderate weight loss and regular physical activity has been shown to improve glycaemic control. [Grade A]
2. The use of anti-obesity agents in these patients is an effective option for those who fail lifestyle intervention. [Grade A]
3. Bariatric surgery may be considered in those who fulfill the strict criteria. [Grade A]
4.1 Hypoglycaemia

Definition

- Hypoglycaemia is defined by either one of the following two conditions: ²²³ (Level III)
  a) Low plasma glucose level (<4.0 mmol/L).
  b) Development of autonomic or neuroglycopenic symptoms (Table 32) in patients treated with
     insulin or OADs which are reversed by caloric intake.

Table 32: Symptoms of Hypoglycaemia

<table>
<thead>
<tr>
<th>Autonomic</th>
<th>Neuroglycopenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trembling</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Confusion</td>
</tr>
<tr>
<td>Sweating</td>
<td>Weakness</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Hunger</td>
<td>Vision changes</td>
</tr>
<tr>
<td>Nausea</td>
<td>Difficulty speaking</td>
</tr>
<tr>
<td>Tingling</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Weakness</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
</tr>
</tbody>
</table>

Table 33: Severity of Hypoglycaemia

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Autonomic symptoms are present. The individual is able to self-treat.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.</td>
</tr>
<tr>
<td>Severe</td>
<td>Individual requires assistance of another person. May become unconscious, plasma glucose is usually less than 2.8 mmol/L.</td>
</tr>
</tbody>
</table>

Figure 6: Hypoglycaemic Symptoms Based on Blood Glucose Levels

• Risk factors for hypoglycaemia include:
  a) Advancing age
  b) Severe cognitive impairment
  c) Poor health knowledge
  d) Increased A1c
  e) Hypoglycaemia unawareness
  f) Long standing insulin therapy
  g) Renal impairment
  h) Neuropathy

Treatment of Hypoglycaemia
• Patients at high risk for severe hypoglycaemia should be informed of their risk and counselled, along with their family members and friends. Patients at risk of hypoglycaemia are discouraged from driving, riding, cycling or operating heavy machineries, as these activities may endanger oneself and the public.

• The aims of treatment are to: 225-227 (Level II-3)
  a) detect and treat a low blood glucose level promptly.
  b) eliminate the risk of injury to oneself and to relieve symptoms quickly.
  c) avoid overcorrection of hypoglycaemia especially in repeated cases as this will lead to poor glycaemic control and weight gain.

• In mild to moderate hypoglycaemia where the individual is able to self-treat, he/she should ingest 15 grams of simple carbohydrate (e.g 1 tablespoon of honey, ¾ cup of juice, 3 teaspoon of table sugar) and repeat blood glucose after 15 minutes. If the level at 15 minutes is still <4.0 mmol/L, another 15 grams of carbohydrate should be taken.

• In severe hypoglycaemia where the individual is still conscious, he/she should ingest 20 grams of carbohydrate and the above steps are repeated.

• In severe hypoglycaemia and unconscious individual, he/she should be given 20–50 mL of D50% intravenously over 1–3 minutes. Outside the hospital setting, a tablespoon of honey should be administered into the oral cavity.

• Once hypoglycaemia has been reversed, the patient should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycaemia.

• Patients receiving anti-diabetic agents that may cause hypoglycaemia should be counselled about strategies for prevention, recognition and treatment of hypoglycaemia. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk.

Hypoglycaemia Unawareness
• Hypoglycaemia unawareness occurs when the ability to perceive the onset of hypoglycaemia is either diminished or completely lost at the physiological plasma glucose concentration at which warning symptoms normally occur. Repeated hypoglycaemia blunts symptomatic and hormonal responses to subsequent episodes leading to hypoglycaemia unawareness.

• Hypoglycaemia unawareness increases the incidence of severe hypoglycaemia by 17-fold for T2DM patients. 228 (Level III)
Hypoglycaemia unawareness should trigger re-evaluation of the treatment regimen. Patients with hypoglycaemia unawareness should be advised to increase their glycaemic targets to strictly avoid further hypoglycaemia for at least several weeks, to partially reverse hypoglycaemia unawareness and to reduce risk of future episodes.

**Nocturnal hypoglycaemia**

- The incidence of nocturnal hypoglycaemia events is difficult to measure because many events are asymptomatic, unrecognised and unreported, partly due to lack of self-monitoring at night time. \(^{(229)}\) (Level III)

- In a study using continuous glucose monitoring (CGM) in T2DM, nearly three-fourth of all hypoglycaemic events occurred at night-time. \(^{(230)}\) (Level II-2)

- This risk is higher especially in the elderly. In elderly diabetic, it was demonstrated that 69% experienced more than one nocturnal hypoglycaemic events, with an average duration of 56 minutes and none was recognised by the patients. \(^{(231)}\) (Level II-3)

- Both physiologic and behavioural defences against hypoglycaemia have been shown to be further compromised during sleep. This explains the high frequency of nocturnal hypoglycaemia seen in diabetic patients. \(^{(232)}\) (Level III)

- The clinical manifestations are vague, and may include: \(^{(233,234)}\) (Level III)
  a) poor sleep quality
  b) vivid dreams or nightmares
  c) waking with chills or sweating
  d) morning headache
  e) chronic fatigue
  f) mood changes and
  g) nocturnal convulsions

- Undetected nocturnal hypoglycaemia can promote hypoglycaemia unawareness, blunt counterregulatory responses, create anxiety, reduce quality of life and increase treatment costs. \(^{(235)}\) (Level II-3) It can also result in negative outcomes such as falls, accidents and arrhythmias.

**Hypoglycaemia and Cardiovascular Disease**

- Cardiovascular disease has been shown to be the most common cause of death (52%) in patients with T2DM. \(^{(236)}\) (Level III)

- More recently, hypoglycaemia has also been shown to exert several CV effects \(^{(237,238)}\) (Level III) and some studies have suggested a link between hypoglycaemic events and CVD in T2DM patients. \(^{(237,239)}\) (Level III)

- Hypoglycaemia causes a cascade of physiological effects and may induce cardiac arrhythmias \(^{(240)}\) (Level III) contributing to increase CVD risk and sudden cardiac death.

- During an acute hypoglycaemic episode, heart rate and systolic blood pressure increase, blood flow increases in the myocardium, cardiac output, stroke volume, and myocardial contractility increase, adding stress to the CV system.

- Hypoglycaemia can also induce changes in the conduction system of the heart, including prolonging the QTc interval \(^{(241,242)}\) (Level III) lengthening repolarisation, and causing ST wave changes. \(^{(240)}\) (Level III)
These cardiac rhythm disturbances may result in sudden cardiac death observed during hypoglycaemia.

- In three major trials (ACCORD, ADVANCE and VADT) more episodes of hypoglycaemia were observed in the intensively treated arms. In particular, the ACCORD trial was associated with a significant increase in mortality.

- Several explanations were postulated to explain the findings in ACCORD, but the most obvious factor was hypoglycaemia, which was threefold higher in the intensive arm. However, it remains unknown whether hypoglycaemia was the direct cause of increased mortality.

- In VADT, hypoglycaemia was found to be a strong predictor for cardiovascular mortality and admission for heart failure.

### Recommendations: Hypoglycaemia

| 1. | Patients with frequent hypoglycaemia are prohibited from driving, riding, cycling or operating heavy machinery. [Grade C] |
| 2. | Patients must be educated on symptoms, risks and treatment of hypoglycaemia. [Grade C] |
| 3. | Hypoglycaemia unawareness should trigger re-evaluation of the treatment regimen. [Grade C] |
| 4. | In patients with hypoglycaemia unawareness and those with concomitant cardiovascular disease, the glycaemic target should be loosened. [Grade B] |

#### 4.2 Diabetic Ketoacidosis (DKA)

- Diabetic ketoacidosis (DKA) is among the most serious acute complications of diabetes.

- It has a high mortality rate if unrecognised. The overall mortality is <1%, but a mortality rate >5% in the elderly has been reported. (Level II-3)

- Precipitating factors should be actively sought out: infection, missed therapy, acute coronary syndrome, CVA, surgery etc.

- Diagnostic criteria:
  All three must be met: (Level III)
  - a) Capillary blood glucose >11 mmol/L
  - b) Capillary ketones >3 mmol/L or urine ketones ≥2+
  - c) Venous pH <7.3 and/or bicarbonate <15 mmol/L

- High-dependency unit (HDU) admission and insertion of central line may be required in the following circumstances:
  - a) Elderly
  - b) Pregnant ladies
  - c) Heart or kidney failure
  - d) Other serious comorbidities
  - e) Severe DKA by following criteria:
    - i. Venous bicarbonate <5 mmol/L
    - ii. Blood ketones >6 mmol/L
    - iii. Venous pH <7.1
    - iv. Hypokalaemia on admission (<3.5 mmol/L)
    - v. Glasgow Coma Scale (GCS) <12
    - vi. Oxygen saturation <92% on air (arterial blood gases required)
iv. Systolic BP <90 mm Hg
viii. Pulse >100 or <60 beats/minute
ix. Anion gap >16 [Anion Gap = (Na⁺ + K⁺) – (Cl⁻ + HCO₃⁻)]

Algorithm 7: Principles of Management

1st Hour: Immediate Management

Step 1. Commence 0.9% saline drip using large bore cannula.
   (See box below for rate of fluid replacement)

Step 2. Commence a fixed rate intravenous insulin infusion (IVII)
   (0.1 unit/kg/hr based on estimate of weight).
   50 units short-acting human insulin made up to 50 mL with
   0.9% saline solution.

Step 3. Assess patient
   • BP
   • Pulse
   • Temperature
   • Respiratory rate
   • Oxygen saturation
   • Glasgow Coma Scale
   • Hydration status
   • Full clinical examination

Step 4. Investigations
   • Capillary and venous blood glucose
   • Arterial blood gases
   • Blood or urinary ketones
   • BUSE
   • FBC
   • Blood cultures
   • MSU
   • ECG (if indicated)
   • CXR (if indicated)

Step 5. Outline monitoring regimen
   • Hourly capillary blood glucose
   • Vital signs and input-output charting hourly
   • Venous bicarbonate and potassium at 60 minutes,
     4 hours and 6-hourly thereafter
   • 6-hourly BUSE and urine ketone
   • Continuous pulse oximetry (if indicated)
   • Continuous cardiac monitoring (if indicated)

Step 6. Look for precipitating causes and treat accordingly
   Start broad-spectrum antibiotics if infection suspected

Initial Fluid & Potassium Replacement

Restoration of circulating volume is a priority

Systolic BP (SBP) <90 mm Hg
Likely to be due to low circulating volume, but consider other
causes such as heart failure, sepsis, etc.

- Give 500 mL of 0.9% saline solution over 10–15 minutes. If
  SBP remains <90 mm Hg, repeat.
- Most patients require between 500-1000 mL with 0.9% saline
  over the next 60 minutes.
- Addition of potassium is likely to be required in the second
  litre of fluid, especially if baseline potassium <5 mmol/L and to
  maintain potassium between 4-5 mmol/L.

Systolic BP on admission ≥90 mmHg
- Give 1000 mL of 0.9% saline for first 60 minutes

Potassium replacement:

<table>
<thead>
<tr>
<th>Potassium level (mmol/L)</th>
<th>Potassium replacement mmol/L of infusion solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5.5</td>
<td>Nil</td>
</tr>
<tr>
<td>3.5–5.5</td>
<td>40 mmol/L (3 g KCL)</td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>Additional potassium required</td>
</tr>
</tbody>
</table>

Caution:
- Withold potassium replacement if no urine output.

Intravenous bicarbonate:
The use of intravenous bicarbonate is not indicated to correct acidosis
in DKA due to:
- Rise in pCO₂ in CSF which may lead to a paradoxical increase
  in CSF acidosis.
- Delay in the fall of blood lactate and ketone level.
- Risk of cerebral oedema especially in younger age groups.
2nd - 6th Hour

Aims of treatment:
- Rate of fall of ketones of at least 0.5 mmol/L/hr, or
- Bicarbonate rise 3 mmol/L/hr, and
- Blood glucose fall 3 mmol/L/hr
- Maintain serum potassium in normal range
- Avoid hypoglycaemia

Step 7. Reassess patient, monitor vital signs
- Hourly blood glucose (lab blood glucose if meter reading ‘Hi’)
- 4-6 hourly blood or urine ketones
- Venous blood gas for pH, bicarbonate and potassium at 60 minutes, followed by 4-6 hourly (depending on the severity of acidosis)
- If potassium is outside normal range, reassess potassium replacement and check 1-2-hourly depending on the severity

Step 8. Continue fluid replacement via infusion pump as follows:
- 1000 mL of 0.9% saline with potassium chloride over next 2 hours
- 1000 mL of 0.9% saline with potassium chloride over next 4 hours
- Once blood glucose falls below 14 mmol/L:
  - Switch to 5% dextrose at 125 mL/hr and reduce insulin infusion rate to 0.06 units/kg/hour; or
  - Switch to 10% dextrose at 125 mL/hr with no change in insulin infusion rate.

More cautious fluid replacement in young people aged under 18 years, elderly, pregnant, have heart or renal failure. (Consider HDU and central line)

6th - 12th Hour

Aims:
- Ensure clinical and biochemical parameters improving
- Continue IV fluid replacement
- Avoid hypoglycaemia
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Treat precipitating factors as necessary

Step 10. Reassess patient, monitor vital signs
- Continue IV fluid at reduced rate
- 1000 mL of 0.9% saline with potassium chloride over 4 hours (continuation from the 5th hour)
- 1000 mL of 0.9% saline with potassium chloride over 8 hours
- Once blood glucose falls below 14 mmol/L:
  - Switch to 5% dextrose at 125 mL/hr and reduce insulin infusion rate to 0.06 units/kg/hour; or
  - Switch to 10% dextrose at 125 mL/hr with no change in insulin infusion rate.

Reassess cardiovascular status at 12 hours; further fluid may be required

Step 9. Assess response to treatment

Insulin infusion rate may need review if:
- Blood ketones not falling by at least 0.5 mmol/L/hr
- Venous bicarbonate not rising by at least 3 mmol/L/hr
- Plasma glucose not falling by at least 3 mmol/L/hr
- Continue fixed rate IV insulin until ketones less than 0.3 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L

If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present.
If equipment is working but response to treatment inadequate, increase insulin infusion rate by 1 unit/hr increments hourly until targets achieved.

Additional measures
- Accurate fluid balance chart, minimum urine output 0.5 ml/kg/hr
- Consider urinary catheterisation if incontinent or anuric (does not pass urine by 60 minutes)
- Nasogastric tube with airway protection if patient obtunded or persistently vomiting
- Measure arterial blood gases and repeat CXR if oxygen saturation less than 92%
- DVT prophylaxis with low molecular weight heparin
- Consider ECG monitoring if potassium abnormal or concerns about cardiac status.

12-24 hours

By 24 hours the ketonaemia and acidosis should have resolved.

Aim:
- Ensure that clinical and biochemical parameters are continuing to improve or are normal
- Continue IV fluid replacement if not eating and drinking
- If ketonaemia cleared and patient is not eating and drinking, titrate insulin infusion rate accordingly
- Reassess for complications of treatment e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors
- Change to subcutaneous insulin if patient is eating and drinking normally

Step 12. Reassess patient, monitor vital signs, review biochemical and metabolic parameters
- At 12 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones <0.3 mmol/L, venous pH >7.3
- If not resolved review Step 9 and Step 10.

If DKA resolved go below
4.3 Hyperglycaemic Hyperosmolar State

• Diagnosis of hyperglycaemic hyperosmolar state (HHS) must be prompt and managed intensively in high-dependency units or equivalent level of care. 249 (Level III)

• The elderly with multiple comorbidities are prone to HHS. However, with the epidemiological shift of T2DM to the younger age group, HHS is often the initial presentation in the younger age group. 250,251 (Level II-3)

• It has a higher mortality than DKA and vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis are common. 252-255 (Level II-3) Well-described complications such as seizures, cerebral oedema and osmotic demyelination syndrome are uncommon. 256,257 (Level III) Rapid changes in osmolality during treatment may also be the precipitant of osmotic demyelination syndrome. 258 (Level III)

• Whilst the presentation of DKA is rapid (within hours), HHS progresses over many days. As a result, the dehydration and metabolic disturbances are more extreme. 259 (Level III)

Diagnostic Criteria of HHS 249 (Level III)

• Hypovolaemia

• Marked hyperglycaemia (BG >30 mmol/L)

• Osmolality >320 mosmol/kg

Other Important Clinical Features 249 (Level III)

• There is no significant hyperketonaemia (<3.0 mmol/L) or acidosis (pH >7.3, bicarbonate >15 mmol/L).

• When acidosis is present, causes of acidosis such as lactic acid and toxicology screen need to be investigated.

• The presence of acute cognitive impairment may be associated with cerebral oedema in severe cases or to the presence of significant electrolyte disturbances, hyperosmolality (>330 mosmol/kg), sudden drop in osmolality, severe dehydration, infection and sepsis, hypoglycaemia during treatment, and renal failure.
Clinical features of dehydration in the patient with HHS can be deceptive and may not be reflective of the seriousness of the fluid depletion. This is because hypertonicity leads to preservation of intravascular volume, causing movement of water from intracellular to extracellular space. 260 (Level III)

Precipitating factors for HHS are:
  a) Infections and sepsis
  b) Thrombotic stroke
  c) Intracranial haemorrhage
  d) Silent myocardial infarction
  e) Pulmonary embolism

Management goals
The goals of treatment of HHS are to treat the underlying cause as well as to gradually and safely:
  • Normalise the osmolality
  • Replace fluid and electrolyte losses
  • Normalise blood glucose
  • Prevention of complications
Algorithm 8: Management of T2DM with Hyperglycaemic Hyperosmolar State

**Principles of treatment**

- Intravenous (IV) 0.9% saline solution is the principle fluid to restore circulating volume and reverse dehydration. Intravenous 0.45% saline solution is only recommended if the osmolality is not declining despite adequate positive fluid balance.

- Monitor serum osmolality regularly to prevent harmful rapid changes in osmolality. (Serum Osmolality =2(Na⁺+K⁺) + Glucose + Urea)

- The rate of rehydration will be determined by assessing the combination of initial severity and any pre-existing comorbidities. Rapid rehydration may precipitate heart failure but insufficient rehydration may fail to reverse acute kidney injury.

- An initial rise in sodium is expected and is not in itself an indication for hypotonic fluids. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.

- The fall in blood glucose should be no more than 5 mmol/L/hr.

- Low dose IV insulin (0.05 units/kg/hr) should be commenced once blood glucose is no longer falling with IV fluids alone or immediately if there is significant ketonaemia (β-hydroxy butyrate >3 mmol/L).

- Prophylactic low molecular weight heparin (LMWH) is recommended unless contraindicated.

- Hyperkalaemia, hypokalaemia, hypophosphataemia and hypomagnesaemia are common and should be corrected accordingly.

- In acutely ill patients, pyrexia may not be present. If sepsis is highly suspicious, the source of infection should be sought and treated.

- Discharge planning includes diabetes education, dietitian referral, education on medication and insulin administration (if patient is on insulin) to reduce the risk of recurrence and prevent long-term complications.

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**Recommendations: Diabetic Ketoacidosis (DKA) and Hyperglycaemic Hyperosmolar State (HHS)**

1. Prompt recognition and institution of treatment are important to avoid complications. *[Grade C]*
2. Severe DKA and HHS should be managed in a high-dependency or intensive care unit. *[Grade C]*
3. Patients must be educated on precipitating factors to avoid DKA or HHS. *[Grade C]*
4. Mainstay of treatment includes restoration of hydration, insulin infusion, correction of electrolytes imbalance and treatment of precipitating cause. *[Grade C]*
5.1 Retinopathy

Introduction

- Prevalence of diabetic retinopathy (DR) is closely linked to the duration of diabetes.

- At diagnosis, less than 5% will have retinopathy while the prevalence rises to 40–50% after 10 years. About 60% patients with T2DM have some degree of retinopathy after 20 years of the disease. 262 (Level III)

- In Malaysia, the prevalence of DR from the 2007 Diabetic Eye Registry was 36.8%. 263 (Level III) However, other unpublished local data obtained from primary care screening centres showed a prevalence ranging between 12.3% and 16.9%. 264,265 (Level III)

- Screening and early treatment can prevent substantial visual loss in many cases.

- The initial assessment should be conducted for all patients at the time of diagnosis of T2DM and annually thereafter. 266,267 (Level III)

- Pregnant women with T2DM should have a retinal examination during each trimester. 268 (Level II-3) DR screening is not required for GDM. 266,269 (Level II-3) However, if GDM is diagnosed in the first trimester of pregnancy, screening should be as per pre-existing DM.

Eye Examination

- Visual acuity is assessed with a Snellen chart and any refractive error corrected with a pinhole in addition to asking the patient to wear bifocals or glasses for presbyopia.

- A non-mydriatic fundus camera should be used as a screening tool for DR. 270 (Level II-2) A two field fundus photo (central and peripheral) assessment should be performed. 270 (Level II-2)

- When there is no access to a fundus camera, an ophthalmoscope should be used for screening DR.

- Tropicamide 1% should be used for pupillary dilatation in selected cases by trained personnel. 270 (Level II)

Treatment

- The mainstay of current treatment involves risk factor modification by tight control of blood glucose, blood pressure and serum lipids. 271-273 (Level I)

- Other modalities of risk factor modification include diet, exercise and smoking cessation. 20 (Level I)

- The presence of retinopathy is not a contraindication to aspirin therapy for cardiovascular disease prevention, as this therapy does not increase the risk of retinal bleeding. 274 (Level I)

- Laser photocoagulation remains the standard practice for treating DR. Stages of DR which require treatment includes severe non-proliferative DR, proliferative DR, advance diabetes eye disease and diabetic macular edema (DME). 275 (Level II)
Referral to an ophthalmologist is necessary for the following situations: 267, 270, 275, 276 (Level III)

a) Severe non-proliferative DR
b) Any level of diabetic maculopathy
c) Any proliferative DR
d) Unexplained visual loss
e) If screening examination cannot be performed including ungradable fundus photo

Vascular endothelial growth factor (VEGF) plays an important role in the development of DME. Anti-VEGF has proven to significantly improved visual acuity and avoid vision loss in patients with DME more often than laser by preventing the blood vessels from leaking fluid and causing macular oedema. 277 (Level III)

Two anti-VEGF drugs, intravitreal ranibizumab and aflibercept are approved by the US FDA and European Medicines Agency (EMA) for treatment of DME. For many patients and clinicians, intravitreal pharmacotherapy with VEGF inhibitors is the initial treatment of choice, but there are few data to guide selection of VEGF inhibitors. Potential adverse effects of VEGF inhibitors include transient increases in intraocular pressure and injection-related infectious endophthalmitis. 278 (Level I)

Table 34: Criteria for Urgent Referral

<table>
<thead>
<tr>
<th>Urgency of Referral</th>
<th>Ocular Features</th>
</tr>
</thead>
</table>
| Emergency (same day referral) | Sudden severe visual loss
| | Symptoms or signs of acute retinal detachment
| Appointment within 1 week | Presence of retinal new vessels
| | Preretinal haemorrhage
| | Vitreous haemorrhage
| | Rubeosis iridis
| Appointment within 4 weeks | Unexplained drop in visual acuity
| | Any form of maculopathy
| | Severe NPDR
| | Worsening retinopathy

Adapted from Screening of Diabetic Retinopathy. Malaysia: Ministry of Health Malaysia and Academy of Medicine Malaysia, 2011. 270 (Level III)

**Recommendations: Retinopathy**

1. The initial assessment should be conducted at the time of diagnosis of T2DM and annually thereafter. [Grade C]
2. Examination schedule and urgency of referral to an ophthalmologist should be based on the grade and severity of diabetic retinopathy as well as the presence of risk factors. [Grade C]
5.2 Nephropathy

Introduction

- Diabetic nephropathy (DN) is a major cause of chronic kidney disease (CKD) contributing to 58% of new patients requiring dialysis in 2012. \(^{279}\) (Level II) DN is also a major risk factor for cardiovascular morbidity and mortality.

- The diagnosis of DN is made clinically by the presence of proteinuria (either microalbuminuria or overt proteinuria). "Moderately increased albuminuria" and "severely increased albuminuria" are new terms for microalbuminuria and overt proteinuria respectively.

- Progression to end stage renal disease (ESRD) requiring renal replacement therapy occurs in many patients, particularly those with poor diabetic and blood pressure control.

Screening

- A standard urine dipstick test for proteinuria should be performed in all diabetic patients at diagnosis and annually. If the test is negative, it is recommended to screen for microalbuminuria using the first morning urine sample or a random urine sample without excessive water intake. \(^{280}\) (Level III)

- Microalbuminuria refers to the presence of a small amount of albumin in the urine which cannot be detected with the usual urine dipstick.

- Microalbuminuria is the earliest sign of diabetic nephropathy and predicts increased cardiovascular mortality and morbidity and end-stage renal failure. \(^{280,281}\) (Level III) If microalbuminuria is detected, a repeat test should be done within 3 to 6 months for confirmation. If it is negative, annual screening should be continued.

- A more sensitive and specific test called the Urine-Albumin Creatinine Ratio (ACR) may be performed in those with negative microalbuminuria. \(^{282}\) (Level III) It is defined as a urinary albumin:creatinine ratio >2.5 mg/mmol in men and >3.5 mg/mmol in women, which is equivalent to a 24-hour urine collection level of >20 mg/L. This should be performed on an early morning urine sample to minimise the effect of posture and exercise on urine albumin excretion.

- Measure serum creatinine at least annually in all adults with diabetes regardless of the degree of urine albumin excretion. The serum creatinine should be used to estimate GFR and stage the level of chronic kidney disease (CKD), if present. \(^{283}\) (Level III)

- Measurement of GFR easily performed by using the CKD-EPI formula which can be accessed at http://www.kidney.org/professionals/KDOQI/gfr_calculator.

Recommendations: Screening for Nephropathy

1. Screening for proteinuria should be performed at diagnosis and annually with a conventional dipstick on an early morning urine specimen. [Grade C]
2. If urine dipstick for proteinuria is negative, screening for microalbuminuria should be performed. [Grade C]
3. If microalbuminuria is detected, confirmation should be made with a repeat test within 3 to 6 months. [Grade C]
4. If microalbuminuria is not detected, re-screening should be performed annually. [Grade C]
5. Regardless of the degree of proteinuria, serum creatinine level should be measured annually to determine GFR. [Grade C]
Management

Blood pressure and glycaemic control are crucial in preventing the progression of diabetic nephropathy.\textsuperscript{171,178,284,285 (Level I)} Dose adjustment of anti-diabetic agents may be necessary in CKD. (Please refer to **APPENDIX 6**)

Proteinuria is an independent predictor for nephropathy progression. The magnitude of proteinuria, measured by 24-hour urine collection, has a linear relationship with progression of nephropathy and risk of CV events. \textsuperscript{284, 184 (Level I), 286 (Level II-2)}

The presence of microalbuminuria or overt proteinuria should be treated even if the BP is <135/75 mm Hg. An ACEI or ARB is preferred. \textsuperscript{182,184,186,287-290 (Level I)} In a proportion of patients, microalbuminuria may be normalised by ACEIs \textsuperscript{289 (Level I)} or ARBs \textsuperscript{290 (Level I)} even if the BP is optimally controlled with close monitoring of potassium levels. Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate. \textsuperscript{182 (Level I)}

Urine protein-creatinine index (UPCI) or ACR should be used to monitor treatment directed against proteinuria.

Decrease protein intake to 0.8 g/kg body weight per day in individuals with diabetes at stage 3 and 4 CKD and to 0.6–0.75 g/kg body weight per day in ESRD. Reduction in protein intake may delay progression of renal impairment. \textsuperscript{291 (Level I)}

Other measures include lipid control, smoking cessation, weight reduction and salt restriction.

**Table 35: Stages of CKD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m² BSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage* with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage* with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>End-stage renal disease</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; BSA = body surface area

* Kidney damage defined as abnormalities on pathological, urine, blood, or imaging tests.

Referral to Nephrologist

(Adapted from Malaysian Clinical Practice Guidelines for the Chronic Kidney Disease in Adults) \textsuperscript{293 (Level III)}

A patient with diabetic kidney disease with the following criteria should be referred to a nephrologist:

- Estimated GFR <30 mL/min or serum creatinine >200 µmol/L
- Heavy proteinuria (urine protein ≥3 g/day or urine protein: creatinine ratio (uPCR) ≥0.3 g/mmol)
- Haematuria
- Rapidly declining renal function (loss of glomerular filtration rate/GFR >5 mL/min/1.73 m² in one year or >10 mL/min/1.73 m² within five years)
- Resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
- Suspected renal artery stenosis
g) Other suspected causes of CKD (primary glomerular disease, genetic or uncertain causes of CKD)
h) Pregnant or when pregnancy is planned

Recommendations: Management of Nephropathy

1. ACEIs or ARBs should be initiated in patients with microalbuminuria or proteinuria. [Grade A]
2. Urine protein-creatinine index (UPCI) or ACR should be used to monitor treatment directed against proteinuria. [Grade C]
3. Protein restriction should be instituted according to degree of renal impairment. [Grade C]

5.3 Neuropathy

Introduction
The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse. The most prevalent neuropathies are peripheral neuropathy (DPN) and autonomic neuropathy (DAN), particularly cardiovascular AN (CAN).

Diabetic peripheral neuropathy

• Diabetic peripheral neuropathy (DPN) may be defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.” 294 (Level III)

• DPN may be asymptomatic in a large proportion of cases (up to 50%) 295 (Level III) and requires clinical examination to document/unveil its existence. It causes or contributes to significant morbidity and mortality. 294,295 (Level III)

• Studies from tertiary centres showed that prevalence of DPN ranged between 50 to 80%. 296,297 (Level II-3)

Screening and Diagnosis
Neuropathy should be assessed with:

• 10-g monofilament; and one other modality:
  a) pin prick
  b) vibration sense using a 128-Hz tuning fork
  c) ankle reflexes
  d) vibration perception threshold testing using a biothesiometer

• The above increases the sensitivity of detecting peripheral neuropathy by 87%. 298-301 (Level II-3)

• These bedside tests should be repeated at least annually.

Treatment

• Tight glycaemic control has not shown any benefit in preventing DPN but has modest effect in slowing progression without neuronal loss reversal.

• No pharmacological therapy has been shown to be effective in treating DPN.

• Drugs approved for pain associated with DPN include pregabalin, gabapentin, amitriptyline, duloxetine and venlafaxine as first line therapy; tramadol as a second line therapy. 302 (Level III) Topical treatment (e.g. capsaicin cream, lidocaine 5% patch) may be added to systemic treatment at any time. 303 (Level III)
Diabetic Autonomic Neuropathy

- Diabetic autonomic neuropathy (DAN) results in significant morbidity and may lead to mortality in some patients with diabetes. CAN, in particular, is an independent risk factor for cardiovascular mortality. 304,305 (Level I)

- Clinical manifestations of DAN include:
  a) resting tachycardia
  b) exercise intolerance
  c) orthostatic hypotension
  d) gastroparesis, constipation
  e) erectile dysfunction
  f) sudomotor (sweat glands) dysfunction
  g) impaired neurovascular function
  h) autonomic failure in response to hypoglycaemia

Treatment

- Intensive control of cardiovascular modifiable risk factors have been shown to reduce the progression and development of CAN among patients with T2DM. 306 (Level I)

- Avoid drugs causing orthostatic hypotension. Midodrine has been approved as medical therapy for orthostatic hypotension. 4 (Level III)

- Prokinetic agents such as erythromycin aid in relieving gastroparesis symptoms.

- Short term metoclopramide (maximum for 5 days) may be used in severe cases. 4 (Level III)

5.4 Coronary Heart Disease

Introduction

- T2DM is associated with increased risk of CHD, manifesting as angina, myocardial infarction (MI), congestive cardiac failure (CCF) and sudden death. In addition, T2DM may lead to diabetic cardiomyopathy. CHD accounts for up to two-thirds of deaths associated with T2DM.

- The increased risk of CHD in diabetic patients is only partly explained by concomitant risk factors such as dyslipidaemia, hypertension, smoking and obesity. Hyperglycaemia itself and its consequences are highly linked to the increased risk of CHD and its related mortality. 27,307,308 (Level II-1)

- CHD in T2DM is characterised by its early onset, extensive disease at the time of diagnosis, and higher morbidity and mortality after MI. Angiographic findings in diabetes are more diffuse, involving multiple coronary arteries including small and distal vessels. 309 (Level II-2), 310,311 (Level I)

Recommendations: Neuropathy

1. Assessment for peripheral neuropathy should be performed at diagnosis and repeated annually. [Grade C]

2. Drugs approved for neuropathic pain include pregabalin, gabapentin, amitriptyline, duloxetine and venlafaxine as first line therapy; tramadol as a second line therapy. [Grade C]

3. Tight control of blood sugar and cardiovascular risks have been shown to reduce the progression and development of autonomic neuropathy. [Grade B]
• Among those above the age of 60, there is a similar occurrence of MI in T2DM patients and in those without T2DM who had previous MI, thus giving rise to the notion that T2DM is a CHD-defining disease. As such, we should manage cardio-metabolic risks associated with T2DM and CHD in T2DM aggressively. \(^{312,313}\) (Level II-2)

**Screening**

• Typical symptoms of CHD warrant a prompt referral to a cardiologist for further assessment. However, it is quite common for patients with T2DM to have atypical symptoms or even ‘silent’ CHD. Atypical symptoms include dyspnoea, fatigue, and gastrointestinal symptoms associated with exertion. \(^{314}\) (Level II-1)

• In asymptomatic patients, routine screening for coronary artery disease is not recommended because it does not improve outcome as long as cardiovascular disease risk factors are treated. \(^{315}\) (Level I)

• In asymptomatic patients whose cardiovascular risk factors are not to target, a CVD risk calculator such as Framingham Risk Score (FRS) or SCORE should be applied. If the scores fall into the high or intermediate risks, every effort should be made to further intensify management of the CVD risk factors. \(^{315}\) (Level I)

• T2DM patients with peripheral or cerebrovascular disease should be screened for CHD. \(^{312,313}\) (Level I)

**Recommendations: Coronary Heart Disease**

1. In asymptomatic patients, routine screening for coronary artery disease is not recommended. [Grade A]

2. In asymptomatic patients whose cardiovascular risk factors are not to target, a CVD risk calculator such as FRS or SCORE should be applied. If the scores fall into the high or intermediate risks, every effort should be made to further intensify the management of CVD risks. [Grade A]

**Aspirin for Primary Prevention of Cardiovascular Disease in People with Diabetes**

• There is strong evidence that aspirin is effective for secondary prevention of cardiovascular events. \(^{316}\) (Level I) However, it is unclear whether it prevents primary cardiovascular events in people who are at high risk of CVD, such as those with T2DM.

• Six well-controlled trials, including the Women’s Health Study and Physicians’ Health Study, have shown no benefit of aspirin in primary prevention even for at risk patients. \(^{317,318}\) (Level I)

• The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study showed that daily low-dose aspirin taken for more than four years by asymptomatic people with diabetes failed to show a significant effect on broad composite cardiovascular disease endpoints. However, the risk of fatal coronary or cerebrovascular events was significantly decreased in the aspirin group in those above the age of 65. \(^{274}\) (Level I)

• In general, we do not recommend aspirin as primary prevention in patients with T2DM. However, the use of low-dose aspirin (100 mg) in those aged 65 or older has been shown to reduce atherosclerotic events. \(^{274}\) (Level I)
5.5 Cerebrovascular Disease

- Patients with diabetes mellitus have approximately twice the risk of ischaemic stroke compared to those without diabetes. In addition, the risk of stroke associated with diabetes is higher in women than in men. Dyslipidaemia, endothelial dysfunction, and platelet and coagulation abnormalities are among the risk factors that may promote the development of carotid atherosclerosis in diabetics.

- For glycaemic control in a patient admitted with acute stroke, please refer to SECTION 6.1. For further details, please refer to the Malaysian Clinical Practice Guidelines on the Management of Ischaemic Stroke, 2012.

5.6 Diabetic Foot

Introduction

- Foot ulcerations and amputations are major causes of morbidity and mortality in patients with diabetes. The prevalence of diabetic foot ulcer is 15% over the course of the disease, while the prevalence of lower limb amputation was 4.3%.

- Peripheral neuropathy predisposes T2DM patients to ulcerations and vasculopathy retards the healing process.

Risk Factors for Foot Ulcers

a) Previous amputation
b) Past foot ulcer history
c) Peripheral neuropathy
d) Foot deformity
e) Peripheral vascular disease
f) Visual impairment
g) Diabetic nephropathy (especially patients on dialysis)
h) Poor glycaemic control
i) Cigarette smoking

Prevention of foot ulcers

- Foot ulcers usually precede amputated digits and limbs. Hence preventing the first ulcer would reduce the incidence of amputations.

- Prevention starts with examination of the feet (shoes and socks removed) and identifying those at high risk of ulceration.

- At-risk patients are then given relevant education to reduce the likelihood of future ulcers.

- The feet should be examined at least once annually or more often in the presence of risk factors.
- Relevant education for patients: 323 (Level III)
  a) In the presence of feet with reduced sensation, look at feet daily using a mirror to detect early ulcerations.
  b) Wear flat, soft and well-fitting shoes to avoid callusities.
  c) Ensure no foreign objects are in the shoes before putting feet in.
  d) Have one pair of shoes for indoor use.

Management
- An ulcer in a patient with any of the above risk factors will warrant an early referral to a specialist for shared care.
- Ulcers with cellulitis will require antibiotics.
- Trauma induced ulcers with no other risk factors will require the standard wound care and close follow-up until full recovery.
- A multidisciplinary approach is recommended for patients with foot ulcer and high-risk feet (e.g. dialysis patients, those with charcot’s foot, prior ulcers or amputation).

### Recommendations: Diabetic Foot

1. Annual feet examination is recommended to identify individuals who will then require intensive education on self care to avoid ulcers and amputations. [Grade B]
2. A multidisciplinary approach is recommended for patients with foot ulcer and high-risk feet. [Grade B]

5.7 Sexual Dysfunction

5.7.1 Erectile Dysfunction

Introduction
- Erectile dysfunction (ED) is the inability to achieve, maintain or sustain an erection firm enough for sexual intercourse that may result from psychological, neurological, hormonal, arterial, or cavernosal impairment or from a combination of these factors. 324,325 (Level II-3)

- The prevalence of ED among diabetic men varies from 35% to 90%. 326-334 (Level II-3) ED is three times more common in diabetic men and its annual, age-adjusted incidence is doubled compared to nondiabetic men. 335,336 (Level II-1) Compared to non-diabetic men, it occurs 10–15 years earlier in diabetic and tend to be more severe with a poorer quality of life and is less responsive to oral treatment. 336-338 (Level II-3) Diabetic men with ED are 50% more likely to be prescribed penile suppositories or injectables and more than twice as likely to undergo penile prosthesis surgery. 339 (Level II-3)

- Advancing age, duration of diabetes, poor glycaemic control, presence of other diabetic complications, hypertension, hyperlipidaemia, sedentary lifestyle and smoking have been shown to be associated with diabetic ED. All diabetic patients with ED should be screened for IHD. 327,329,338,340-343 (Level II-2)

Screening and Diagnosis
- All adult diabetic males should be asked about ED since many patients do not voluntarily offer the history. 344 (Level II-3) At the same time, they should also be screened for any symptoms or signs of
hypogonadism such as decreased libido, absence of early morning erection, testicular or muscle atrophy. In those with clinical features of hypogonadism, early morning serum testosterone should be performed. 345,346,347 (Level III)

- Genitalia and rectal examination should be carried out to look for anomalies in the penis, scrotum and prostate.

- Screening can be done using the 5-item version of the International Index of Erectile Function (IIEF) questionnaire. 348,349 (Level I) Please refer to APPENDIX 7.

Treatment

- Optimisation of glycaemic control, management of other comorbidities and lifestyle modifications are essential.

- Psychosexual counseling for patient and partner is recommended for the functional, organic and mixed (functional and organic) types of ED, and should be performed by a trained psychologist/psychiatrist.

- Avoid medications that may cause or worsen ED such as thiazides, beta-blockers, calcium channel blockers, methyldopa, H-2 antagonists, spironolactone, ketoconazole, digoxin, amiodarone, tricyclic anti-depressants, SSRIs, phenothiazines, narcotics, and NSAIDs.

- Phosphodiesterase-5 (PDE-5) inhibitors e.g. sildenafil, tadalafil and vardenafil 350-353 (Level I) can be used to treat ED and should be offered as first-line therapy to men with diabetes wishing treatment. PDE-5 inhibitors are contraindicated in unstable angina, poor exercise tolerance or nitrate medication. PDE-5 inhibitors can be of great help to improve the patient's self-esteem.

- Those with confirmed hypogonadism should be treated with IM testosterone as it improves the effect of PDE-5 inhibitors. 347 (Level III)

- Referral to a urologist may be necessary for those not responding to PDE-5 inhibitors.

- Other therapies include intracavernosal injections, intraurethral alprostadil, vacuum devices with constricting band and surgery.

Recommendations: Erectile Dysfunction

1. All adult males with diabetes should be asked about ED. [Grade C]
2. PDE-5 inhibitor should be offered as first-line therapy if there are no contraindications. [Grade A]
3. Referral to a specialist in ED should be considered for men who do not respond to PDE-5 inhibitors or for whom the use of PDE-5 inhibitors is contraindicated. [Grade C]

5.7.2 Female Sexual Dysfunction

Introduction

- Female sexual dysfunction (FSD) is defined as persistent or recurring decrease in sexual arousal, dyspareunia and a difficulty or inability to achieve an orgasm that leads to personal distress and relationship difficulties. 354 (Level III) FSD consist of female sexual interest/arousal disorder, orgasmic disorder and genito-pelvic pain/penetration disorder. 355 (Level III) Most women experience a combination of these disorders.
• FSD is estimated to occur in 24–75% in diabetic women. 356-364 (Level III)

• Age, duration of diabetes, poor glycaemic control, menopause, microvascular complications, and psychological factors (depression and anxiety disorder) have all been associated with sexual dysfunction. 356-360,365,366 (Level II-2)

Screening and Diagnosis

• All diabetic women should be asked about sexual dysfunction.

• A brief sexual symptom checklist can be used as an initial screening.

• The patient’s medical, surgical, social and psychiatric history should also be obtained.

Figure 6: Sexual Symptom Checklist for Women

<table>
<thead>
<tr>
<th>Sexual Symptom Checklist for Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Please answer the following questions about your overall sexual function:</strong></td>
</tr>
<tr>
<td>1. Are you satisfied with your sexual function? Yes / No</td>
</tr>
<tr>
<td><strong>If No, please continue.</strong></td>
</tr>
<tr>
<td>2. How long have you been dissatisfied with your sexual function? __________</td>
</tr>
<tr>
<td>3. Mark which of the following problems you are having, and tick the one that is most bothersome:</td>
</tr>
<tr>
<td>- Little or no interest in sex</td>
</tr>
<tr>
<td>- Decreased genital sensation (feeling)</td>
</tr>
<tr>
<td>- Decreased vaginal lubrication (dryness)</td>
</tr>
<tr>
<td>- Problem reaching orgasm</td>
</tr>
<tr>
<td>- Pain during sex</td>
</tr>
<tr>
<td>- Other: ________________________________</td>
</tr>
<tr>
<td>4. Would you like to talk about it with your doctor? Yes / No</td>
</tr>
</tbody>
</table>


• Diagnosis of FSD can be established by using the FSFI questionnaire that consists of 19 questions covering all domains of sexual dysfunction 368,369 (Level III) available at www.fsfiquestionnaire.com. The validated Malay version is also available. 368,369 (Level III)

• Physical examination should include assessment of thyroid status or galactorrhoea.

• Gynaecological examination should be performed if indicated.

• Oestrogen deficiency is usually detected by history and examination.

• Investigations: Haemoglobin, thyroid, prolactin and gonadotrophins, to rule out metabolic or pituitary dysfunction may be required. 370 (Level III)

• Routine laboratory testing for testosterone and dehydroepiandrosterone (DHEAs) levels are not recommended. 371 (Level III)
Treatment

- Emphasis should be made to treat psychosocial disorders and relationship disharmony.
- Optimisation of glycaemic control.
- Avoid drugs that may affect sexual function:
  a) Beta-blockers, alpha-blockers, diuretics
  b) Tricyclic antidepressants, SSRIs, lithium, neuroleptics
  c) Anticonvulsants
  d) Oral contraceptive pills
- In postmenopausal women, tibolone has been associated with significant increases in sexual desire and arousal. \textsuperscript{372} (Level I) Topical lubricants, vaginal moisturisers and local oestrogen application aid with vaginal dryness and dyspareunia.
- Androgen, DHEAs and PDE5 inhibitor are not recommended. \textsuperscript{371,373} (Level III)

Recommendations: Female Sexual Dysfunction

1. FSD is common and should be screened and managed where appropriate. \textsuperscript{[Grade C]}

5.8 Mental Health Issues in Diabetes

- Rates of depression are increased by 15\% in people with diabetes compared to people without diabetes. \textsuperscript{374,375} (Level II-2) In a study involving 2508 patients with diabetes from 12 health clinics in Malaysia, 11.5\% were found to have depression. \textsuperscript{376} (Level II-2)
- Psychological and social factors are important influences on the ability of patients to cope with chronic disease such as diabetes as they may affect the overall success of management.
- One of the best opportunities to address these are at the time of diagnosis or first presentation. Other times include during scheduled clinic visits and hospitalisations. It is also pertinent to reassess the psychosocial status at diagnosis of complications, when glucose control is out of control and when there are suggestions that compliance to the diabetes regimen has been compromised.
- The pressures of dealing with a chronic and complex condition like diabetes have been associated with a higher incidence of depression. It resulted in reduced quality of life and increased distress levels as self-care management is affected in patients with higher depressive symptoms.
- Depression has been shown to affect glycaemic control and fluctuations in glucose levels can also aggravate depression. Depression and diabetes are also associated with a significantly increased all-cause and CVD-related mortality.
- Symptoms to look for may include the prolonged period of moodiness with any or all of the following:
  a) Appetite changes
  b) Loss of interest in daily activities
  c) Feeling of despair
  d) Inappropriate sense of guilt
  e) Sleep disturbance
  f) Weight loss
g) Suicidal thoughts

- Indications for referral to a mental health specialist may include:
  a) Depression with the possibility of self-harm
  b) Debilitating anxiety (alone or with depression)
  c) Indications of an eating disorder
  d) Cognitive functioning that significantly impairs judgment

- Other psychological issues to look out for are obsession, fear and anxiety, frustration, guilt, embarrassment, non-adherence, pessimism and learned helplessness. Although the doctor may not feel adequate to handle psychological problems, capitalizing on the patient-doctor relationship as a basis for further treatment can increase the likelihood that the patient will readily consent to be referred for psychological management. It is important to acknowledge that mental health well-being is a very important part of diabetes management. 377,378 (Level III)

**Recommendations: Mental Health Issues in Diabetes**

1. Assessment of psychological and social wellbeing should be performed as part of continuing diabetes management; at diagnosis, onset of complications, when diabetes is out of control and whenever indicated. [*Grade C*]
6.1 Management of Type 2 Diabetes Mellitus in Acute Illnesses, Stress and Surgery

• Hyperglycaemia in acute illness may reflect previously known or previously undiagnosed diabetes. Acute illness results in a number of physiological changes (e.g. increases in circulating concentrations of stress hormones) or therapeutic interventions (e.g. glucocorticoid use) that can exacerbate hyperglycaemia. 379 (Level III)

• Hyperglycaemia, in turn, causes physiological changes that can exacerbate acute illness, such as decreased immune function and increased oxidative stress. This leads to a vicious cycle of worsening illness and poor glucose control requiring hospital admission. 379 (Level III)

• A number of studies have demonstrated that inpatient hyperglycaemia is associated with increased morbidity and mortality. 380-383 (Level II-3) Stress hyperglycaemia in a hospital setting is associated with a mortality rate of 11.2%. 384 (Level II-2)

Diagnosis of Diabetes and Stress Hyperglycaemia in the Acute Illness

• Stress hyperglycaemia is defined as any glucose value >7.8 mmol/L in patients with no previous history of diabetes. 385 (Level III)

• Diagnosis of T2DM in an inpatient hospital setting is based on the following: 386 (Level II-3)
  a) History of T2DM
  b) No history of T2DM: BG measurement >7.8 mmol/L and elevated A1c. An elevated A1c without history of T2DM helps to differentiate between newly diagnosed T2DM and stress hyperglycaemia.

Glycaemic Control in Non-critically Ill Patients 387 (Level III)

• There are lack of randomised controlled trials on the benefits and risks of “loose” vs. “tight” glycaemic control in non-critically ill patients. Current recommendations are based on clinical experience and judgment.

• During hospital admission, OADs should be stopped for the following:
  a) Poor oral intake
  b) Acute kidney injury
  c) Exposure to intravenous contrast dye (specifically for those on metformin)
  d) Illness becomes critical
  e) Organ failure e.g. renal failure, liver failure, heart failure

• Stable patients without the above contraindications can often have their home medications continued while in the hospital.

• For those who require insulin therapy, a basal-bolus supplemental insulin regimen may be used. The target for preprandial glucose targets is recommended between 5.0 to 8.0 mmol/L with random BG values <10.0 mmol/L, as long as these targets can be safely achieved without hypoglycaemia.

• If BG values are ≤3.9 mmol/L, the glucose-lowering therapy should be modified, unless the event is easily explained by other factors (e.g. a missed meal).
Glycaemic Control in Critically-ill Patients

- Appropriate glycaemic targets for patients with preexisting diabetes who are critically ill (ICU setting) have not been firmly established. Intensive insulin therapy has been associated with an increased risk of hypoglycaemia and mortality in the ICU setting.\(^{388}\) (Level II-1)

- Therefore, it is recommended to maintain BG levels between 8.0 and 10.0 mmol/L in critically ill patients; a lower BG target (but not <6.0 mmol/L) may be appropriate in post-CABG patients.\(^{389}\) (Level II-3) Insulin infusion protocols with proven efficacy and safety are recommended to minimise the risk of hypoglycaemia.

Table 36: Glycaemic Targets in Critically-ill Patients

<table>
<thead>
<tr>
<th>Patient’s Setting / Condition</th>
<th>Target Range of Glycaemic Control</th>
<th>Management</th>
</tr>
</thead>
</table>
| Intensive care unit          | 7.8-10.0 mmol/L                   | • Intravenous insulin infusion with intensive glucose monitoring  
                               |                                   | • Avoid hypoglycaemia  
                               |                                   | • Treat preclinical condition  |
| Acute myocardial infarction (AMI) | 7.0-10.0 mmol/L                   | • Intravenous insulin infusion with intensive glucose monitoring  
                               |                                   | • Avoid hypoglycaemia  
                               |                                   | • Treatment per AMI  |
| Acute ischaemic stroke       | 7.0-10.0 mmol/L                   | • Avoid hypoglycaemia  
                               |                                   | • Use insulin if OAD(s) cannot achieve target  |
| Congestive cardiac failure (CCF) | 7.0-10.0 mmol/L                   | • Metformin is contraindicated in moderate-severe CCF  
                               |                                   | • As per treatment for heart failure  
                               |                                   | • Glycaemia tend to improve with resolution of heart failure  |
| Diabetic ketoacidosis        | Please refer to Section 4.2       |            |
| Hyperglycaemic hyperosmolar state | Please refer to Section 4.3       |            |

Glycaemic control in major surgery

- Acute hyperglycaemia during major surgery increases postsurgical complications, morbidity and mortality.

- Tight glycaemic control to achieve normoglycaemia while avoiding hypoglycaemia is recommended.
Table 37: Glycaemic Targets in Patients Undergoing Surgery

<table>
<thead>
<tr>
<th>Type and Timing of Surgery</th>
<th>Target Range of Glycaemic Control</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-surgery preparation/post surgery</td>
<td></td>
<td>Monitoring:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OAD/SC insulin: 4-point BG monitoring (pre-meals and bedtime)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin infusion: Hourly BG monitoring</td>
</tr>
<tr>
<td></td>
<td>• Minor or moderate surgery $^{400,401}$ (Level II-1), $^{402}$ (Level I)</td>
<td>5.0–11.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If not controlled: Stop OAD(s), start SC insulin</td>
</tr>
<tr>
<td></td>
<td>• Major surgery $^{403,404}$ (Level II-3)</td>
<td>5.0–10.0 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If not controlled: Stop OAD(s) and start basal bolus during non-fasting state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When fasting: Stop OAD(s) or basal bolus and start insulin infusion</td>
</tr>
<tr>
<td>Intraoperative for all types of surgery $^{403, 402, 405,406}$ (Level II-3)</td>
<td>5.0–10.0 mmol/L</td>
<td>• Insulin infusion and intensive glucose monitoring for prolonged surgery (&gt;4 hours) and those with difficult to control blood glucose levels</td>
</tr>
<tr>
<td>Immediate post-operative for all types of surgery $^{407,408}$ (Level I), $^{409}$ (Level II-1), $^{410}$ (Level II-3)</td>
<td></td>
<td>• Intensive blood glucose monitoring is necessary in the post surgical recovery period</td>
</tr>
<tr>
<td>• Minor or moderate surgery</td>
<td>5.0–10.0 mmol/L</td>
<td>• When tolerating well orally, resume OAD(s)</td>
</tr>
<tr>
<td>• Major surgery</td>
<td>5.0–10.0 mmol/L</td>
<td>• Cease insulin infusion when tolerating orally, start SC insulin and then back to the usual anti-diabetic regime once the wound heals fully.</td>
</tr>
</tbody>
</table>

**Insulin**

- The use of sliding scale insulin (SSI) in the inpatient hospital setting is strongly discouraged. Sliding-scale insulin protocols, which are extensively used, when compared to a basal-bolus regime have been shown to be associated with: (a) increased glycaemic variability; (b) longer time to achieve glycaemic target. $^{411,412}$ (Level I)

**Special Clinical Situations**

**Patients receiving enteral or parenteral feedings** $^{387}$ (Level III)

- In patients receiving parenteral nutrition (PN), insulin can be administered with the PN. An IV infusion of regular insulin is often used initially to estimate the total daily dose (TDD) of insulin required. Depending on the feeding regime, use premixed insulin e.g. 30/70. The TDD is divided by 3 and given three times a day to match the feeding time.

- Alternatively, use a long-acting, less peak basal insulin alone (once-daily glargine or twice daily detemir). For basal-bolus regime, approximately 50% of the TDD is provided as basal insulin and
50% as bolus insulin, which is administered in divided doses. The dose of insulin is adjusted based on BG monitoring results.

- Short-acting human insulin is preferred over rapid-acting insulin analogues because of the longer duration of action. Supplemental insulin should be administered as needed with the bolus insulin. In the event that tube feeds are interrupted, IV dextrose may be required to prevent hypoglycaemia.

Patients receiving corticosteroid therapy
- Corticosteroid therapy can cause hyperglycaemia in 20-50% of patients without a previous history of diabetes. 413 (Level II-3)

- Although the optimal management of hyperglycaemia in patients receiving high-dose oral corticosteroids has not been clearly defined, glycaemic monitoring for at least 48 hours is recommended for patients with or without a history of diabetes. 385 (Level II-3)

- Insulin is generally preferred with an emphasis on adjusting bolus insulin doses and avoiding hypoglycaemia. During the tapering of corticosteroid therapy, insulin dosing should be proactively titrated to prevent hypoglycaemia.

Transition from hospital to home
- During recovery, education on diabetes care including treatment regime, blood glucose monitoring and medical nutritional therapy are important aspects of discharge planning.

Recommendations: Management of T2DM in Acute Illnesses, Stress and Surgery

1. Prompt recognition of hyperglycaemia and prompt institution of treatment are important to avoid complications. [Grade B]
2. Blood glucose levels should be between 8.0 to 10.0 mmol/L in critically ill patients. [Grade B]
3. The use of sliding-scale insulin therapy in inpatient hospital setting is strongly discouraged. [Grade B]

6.2 Diabetes in Pregnancy and Gestational Diabetes Mellitus

Pre-conception Counseling
- Women with diabetes who receive preconception counseling have better pre-conception glycaemic control and are more likely to have favourable pregnancy outcomes. 414 (Level II-2)

- It should be provided by a multidisciplinary team, which includes physician, obstetrician, dietitian, diabetes nurse educator and other health care providers.

- The discussion should include the following points:
  a) Pregnancy has to be planned and to occur only when the woman has good glycaemic control, has had appropriate assessment and management of comorbidities, and has discontinued potentially unsafe medications during pregnancy.
  b) The importance of smoking cessation.
  c) The time, commitment and effort required by the patient in both self-management and engagement with the health care team.
  d) The importance of notifying the health care team without delay in the event of conception.
Pre-pregnancy Management
- Keep the A1c as normal as possible (<6.5%). 415 (Level II-2)
- Weight reduction in those overweight and obese before pregnancy.
- Folic acid supplementation should be started 3 months before withdrawal of contraception. 416 (Level I)
- Women on OAD(s) can be switched to insulin for better glycaemic control before planning pregnancy.
- Insulin treated women should be on multiple daily doses (basal-bolus) of insulin.
  a) Multiple daily doses of short-acting human insulin have been used safely and effectively.
  b) Rapid acting insulin analogues may be used to achieve better 1-hour postprandial glycaemic control with less hypoglycaemia although perinatal outcomes are similar to human insulin. 417 (Level II-1)
  c) Insulin detemir has similar efficacy as NPH insulin but with less nocturnal hypoglycaemia.
  d) Insulin glargine has no RCT data but observational data suggest no adverse effects on pregnancy.
- Screen for diabetic retinopathy and treat appropriately prior to conception. 418 (Level II-2)
- Screen for diabetic nephropathy prior to pregnancy. Women with significantly reduced e-GFR should be counselled by a nephrologist for specific risk of worsening renal function during pregnancy.
- Satisfactory BP control of <130/80 mm Hg before pregnancy is necessary. Common medications used in diabetes such as ACE-inhibitors and ARB should be discontinued upon confirmation of pregnancy. Antihypertensive medications safe to use during pregnancy are methyldopa, labetalol, nifedipine, diltiazem and prazosin.
- Statin should be discontinued during pregnancy as the safety is not known.
- Patient with multiple cardiovascular risk factors should undergo CV risk assessment prior to withdrawal of contraception. Myocardial infarction during pregnancy is associated with adverse maternal and foetal outcomes. 419 (Level III)

Gestational Diabetes Mellitus
- Gestational diabetes mellitus (GDM) is any degree of glucose intolerance which is first recognised during pregnancy, whether or not the condition persisted after pregnancy.
- The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that risk of adverse maternal, foetal, and neonatal outcomes continuously increased as a function of maternal glycaemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. 420 (Level I)

Screening and Diagnosis for GDM
- In view of the increasing prevalence of T2DM in the country and the significance of the HAPO study, we recommend that all pregnant women should be screened for GDM. This universal screening should be performed between week 24 to 28 of gestation using modified OGTT (mOGTT). However, in facilities where this is not feasible due to factors such as cost and limited resources, the
recommendation to screen individuals at high risk of developing GDM at booking should be adhered to.

• In general, screening should be done at booking for any pregnant women who have the following risk factors:
  a) BMI >27 kg/m²
  b) Previous macrosomic baby weighing ≥4 kg
  c) Previous gestational diabetes mellitus
  d) First-degree relative with diabetes
  e) History of unexplained intrauterine death
  f) History of congenital anomalies
  g) Glycosuria at the first or any prenatal visit
  h) Current obstetric problems (essential hypertension, pregnancy-induced hypertension, polyhydramnios and current use of steroids)

• Initial screening of high-risk women at booking can be performed using any of the following:
  a) 75-g mOGTT, with 0’ and 120’ plasma glucose measurements
  b) Fasting plasma glucose (FPG)

• In those who have the above risk factors and initial screening results are normal, a repeat mOGTT should be performed 4–6 weeks later. 4,421 (Level I)

• A single abnormal result is sufficient to confirm the diagnosis. A repeat test is not advocated.

• There is no benefit in differentiating between pre-existing T2DM and GDM as their management and treatment goals during pregnancy are the same. This issue should be addressed during the postpartum period.

Table 38: Diagnostic Criteria for GDM

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>FPG (mmol/L)</th>
<th>2-h Value (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes mellitus</td>
<td>≥5.1*</td>
<td>≥7.8**</td>
</tr>
</tbody>
</table>

* Adapted from the American Diabetes Association–Standards of Medical Care in Diabetes–2015, 4 (Level III). The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management and care, 422 (Level III) International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations on the diagnosis and classification of hyperglycemia in pregnancy, 423 (Level III) and World Health Organization (WHO): Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy. 424 (Level III)

** Adapted from NICE Guidance on Diabetes in Pregnancy: Management of Diabetes and its Complications from Preconception to the Postnatal Period, 2015. 421 (Level III). These levels are adopted in view of the fact that T2DM is diagnosed in Asians at lower A1c, body mass index and waist circumference levels compared to the West.

Management of diabetes in pregnancy

Nutrition
• It is important for patients to receive medical nutrition therapy defined as a carbohydrate controlled meal plan that promotes adequate nutrition with appropriate weight gain, normoglycaemia and the absence of ketosis.

Weight Management
• Energy prescription should be individualised based on pre-pregnancy body weight.
a) For women with normal pre-pregnancy weight, caloric prescription should be as per normal pregnancy (35 kcal/kg body weight).

b) For overweight/obese women, moderate caloric restriction (25 kcal/kg body weight) is advocated without inhibiting foetal growth, birth weight or inducing ketosis. 4 (Level I)

c) Carbohydrate intake should be limited to 45% of total calories.

d) Recommended weight gain is shown in Table 40.

Table 39: Total Weight Gain and Rate of Weight Gain During Pregnancy

<table>
<thead>
<tr>
<th>Pre-pregnancy BMI</th>
<th>Total Weight Gain (Range, kg)</th>
<th>Rates of Weight Gain in 2nd and 3rd Trimester [Mean (Range), kg/wk]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>12.5-18.0</td>
<td>0.51 (0.44-0.58)</td>
</tr>
<tr>
<td>Normal weight (18.5-24.9 kg/m²)</td>
<td>11.5-16.0</td>
<td>0.42 (0.35-0.50)</td>
</tr>
<tr>
<td>Overweight (25.0-29.9 kg/m²)</td>
<td>7.0-11.5</td>
<td>0.28 (0.23-0.33)</td>
</tr>
<tr>
<td>Obese (≥30 kg/m²)</td>
<td>5.0-9.0</td>
<td>0.22 (0.17-0.27)</td>
</tr>
</tbody>
</table>

• Adapted from the National Academies Collection: Weight Gain During Pregnancy: Reexamining the Guidelines, 2009. 425 (Level III)

Insulin therapy

• Insulin therapy should be considered if the blood glucose targets are not met 1-2 weeks after introducing changes to diet and initiating exercise. 421 (Level III)

• The best insulin regime is multiple daily injections for better glycaemic control during pregnancy.

• In the first trimester there is often a decrease in the total daily dose of insulin. In the second trimester, rapidly increasing insulin resistance requires a biweekly increase in insulin dose to achieve glycaemic targets. 4 (Level III)

• Long-acting insulin analogues may be used in cases of repeated nocturnal hypoglycaemia. 426 (Level I)

• Patients who are admitted for short-term corticosteroid therapy should be monitored closely for any abnormal glucose levels and insulin should be instituted when indicated.

Table 40: Initiating Insulin Therapy in Pregnancy

<table>
<thead>
<tr>
<th>Glycaemic Abnormality</th>
<th>Suggested Insulin Type and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG &gt;5.3 mmol/L</td>
<td>• Start 0.2 units/kg of intermediate-acting insulin at bedtime, increase by 2 units every 3 days until targets are reached.</td>
</tr>
<tr>
<td>1-hour postprandial &gt;7.8 mmol/L</td>
<td>• Start 6 units of short-acting insulin, increase by 2 units every 3 days until targets are reached.</td>
</tr>
<tr>
<td>2-hour postprandial &gt;6.7 mmol/L</td>
<td>• If pre-prandial short-acting insulin dose exceeds 16 units TDS, consider adding 6-10 units intermediate-acting insulin in the morning and titrate accordingly until targets are achieved.</td>
</tr>
</tbody>
</table>
Self-monitoring of blood glucose (SMBG)

- Important in all pregnant women with GDM.
- Monitoring should be done at the following times (spread out over a few days):
  a) Fasting (following an 8-hour of overnight fast) and before each meal.
  b) 1 or 2 hours after the start of each meal (post-prandial).
  c) Bedtime and during the night if indicated.
- More frequent monitoring is essential in those who are poorly controlled.
- Monitoring should preferably be done at home. The traditional blood sugar profile (BSP) performed in the hospital may not reflect the actual day-to-day blood sugar levels.

Table 41: Blood Glucose Targets in Pregnancy

<table>
<thead>
<tr>
<th>Timing of Blood Glucose</th>
<th>Target Value (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting or pre-prandial</td>
<td>≤5.3</td>
</tr>
<tr>
<td>1 hour after the start of a meal</td>
<td>≤7.8</td>
</tr>
<tr>
<td>2 hours after the start of a meal</td>
<td>≤6.7</td>
</tr>
</tbody>
</table>

- Adapted from the American Diabetes Association–Standards of Medical Care in Diabetes–2015, 4 (Level III) NICE Guidance on Diabetes in Pregnancy: Management of Diabetes and its Complications from Preconception to the Postnatal Period, 2015, 421 (Level III) and the International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management and care, 422 (Level III)

OAD therapy

- Published data suggest that the use of metformin in GDM is not associated with any birth defects, pre-eclampsia or any adverse maternal nor foetal outcomes.
- Based on two recent systematic analysis and meta-analysis, the use of metformin in GDM leads to better maternal outcomes in terms of total weight gain, postprandial blood glucose and pregnancy-induced hypertension; while foetal outcomes were better in terms of severe neonatal hypoglycaemia but worse in terms of preterm birth. Among these variables, weight gain, pregnancy-induced hypertension and neonatal hypoglycaemia were considered highest priority in evaluating the role of metformin in GDM. 427-429 (Level I)
- The use of metformin during pregnancy in women with polycystic ovarian syndrome is associated with reductions in miscarriage in early pregnancy, weight, fasting serum insulin levels and the incidence of gestational diabetes. 421 (Level III)
- In view of the above findings, metformin may be offered to well-informed pregnant women after discussion on the safety and the off label use of it.
- The use of glibenclamide in GDM is associated with increased risk of neonatal hypoglycaemia, high maternal weight gain and macrosomia. 428 (Level I)

Intrapartum

- Monitor capillary plasma glucose every hour to maintain blood glucose levels between 4-7 mmol/L.
- Insulin infusion should be initiated if the capillary blood glucose is not maintained between 4-7 mmol/L. 421 (Level III)
Post partum

• Insulin requirements drop immediately after delivery by 60-75%. [430 (Level III)]

• When breastfeeding, if glycaemic control is inadequate with diet therapy alone, insulin therapy should be continued at a lower dose.

• Most women diagnosed with GDM should be able to discontinue their insulin immediately after delivery.

• In non-breastfeeding mothers, OAD agents can be continued.

• Low dose metformin can be safely used in nursing mothers. [82 (Level II-2)]

• Patients should be counselled regarding appropriate contraception.

• Those whose blood sugar normalised immediately after delivery should have a mOGTT performed 6 weeks later. A1c may be falsely elevated in those who are taking iron supplements.

• Women should be informed of the risk of GDM in future pregnancies and advised to have a mOGTT when planning future pregnancies.

• Women with a history of GDM should have annual screening for diabetes. Lifestyle modifications or metformin therapy post-GDM has been shown to prevent the development of diabetes. [431 (Level I)]

### Recommendations: Diabetes in Pregnancy and Gestational Diabetes Mellitus

1. A1c of <6.5% should be targeted before and during pregnancy for those with a history of diabetes. [Grade C]

2. Universal screening should be performed on all pregnant women between week 24 to 28 of gestation using mOGTT. However, in facilities where this is not feasible, recommendation no. 3 below should be adhered to. [Grade C]

3. Women with risk factor(s) for diabetes should be screened at booking. If the result is normal, mOGTT should be performed 4-6 weeks later. [Grade C]

4. For better glycaemic control during pregnancy, the best insulin regime is multiple daily injections. [Grade C]

5. The glycaemic targets are ≤5.3 mmol/L, ≤7.8 mmol/L and ≤6.7 mmol/L for pre-prandial, 1-hr post-meal and 2-hr post-meal, respectively. [Grade C]

6. Those whose blood sugar normalised immediately after delivery should have a mOGTT performed 6 weeks later. [Grade C]

7. Women with a history of GDM should have annual screening for diabetes. [Grade C]

### 6.3 Diabetes Mellitus in Adolescents

Introduction

• T2DM is rapidly increasing among the adolescents (ages 12-18 years) in tandem with rising sedentary lifestyles and prevalence of obesity. It is currently the commonest form of diabetes in this age group in many countries. [432-435 (Level III)] In Japan, the incidence rate of T2DM in children <18 years from 1981 to 1990 has been reported to be 4.1/100,000 person-years compared to 1.5 to 2.0/100,000 person-years for T1DM. [436 (Level III)]
• T2DM usually occur in the second decade coinciding with physiologic pubertal insulin resistance. It is rare in pre-adolescents.

• Ketosis or ketoacidosis is not uncommon at presentation of T2DM among adolescents. This presentation may be responsible for the misclassification of T2DM patients as T1DM. 435,437 (Level III)

• Between 15-40% of T2DM patients have T1DM-associated pancreatic autoantibodies. These patients are less overweight, younger, have higher A1c and more rapid development of insulin dependence (usually by 3 years duration). 438,439 (Level II-2)

• T2DM may be misdiagnosed as T1DM:
  a) in non-obese adolescents with diabetes.
  b) when ketosis/ketoacidosis is present at onset.
  c) when pancreatic autoantibodies are positive.

• Other types of diabetes mellitus may be misdiagnosed as T2DM:
  a) Obese T1DM
  b) T1DM with low autoimmunity
  c) Monogenic diabetes

Screening and Diagnosis
• Adolescents should be screened if they are symptomatic or if they are overweight (BMI >85th percentile for age and sex, or weight >120% of ideal) and have two or more of the following risk factors:
  a) Family history of T2DM in first- or second-degree relative.
  b) Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, PCOS). 440 (Level III)
  c) Maternal history of GDM during child’s gestation.

• Screen every two years starting at the age of 10 or at onset of puberty if puberty occurs at a younger age. 441 (Level III) A glucose load of 1.75 g/kg body weight (maximum of 75 g) for OGTT is used.

• Fasting insulin and C-peptide have been used to aid in the diagnosis. However their measurement should be interpreted with caution due to considerable overlap between T1DM, T2DM and monogenic diabetes at onset and within two years of diagnosis.

• The overlap is due to initial recovery phase (honeymoon period) of T1DM, glucotoxicity and lipotoxicity impairing insulin and C-peptide secretion. Such measurements are of little value in the acute phase of the illness. However persistent elevation of C-peptide would be unusual in T1DM after 12-24 months from diagnosis.

• C-peptide should be measured if there is worsening diabetes control in overweight/obese adolescents on oral agents, in order to revise the diabetes classification.

Management
• Management of T2DM in the adolescents should involve the patient and his/her family, emphasising healthy rearing patterns and parental modeling of healthy habits.

• Education and recommendations must be age-appropriate and sensitive to the family’s cultural practices and financial resources.
- Lifestyle changes is the cornerstone of T2DM treatment. Such changes need to be permanent.

- Pharmacotherapy:
  a) Treatment of T2DM in adolescents follow the same rationale as does treatment in adults.
  b) The safety and efficacy of OADs in adolescents have not been established.
  c) Among all the OADs currently used to treat T2DM in adults, only metformin and insulin are FDA approved for use in adolescents <18 years of age.
  d) Metformin should be started with 500 mg daily for 7 days. Gradual dose increment by 500 mg once a week over 3-4 weeks until the maximal dose of 1000 mg BD is achieved.
  e) Insulin may be required for initial metabolic control. Transition from insulin to metformin can usually be made when metabolic stability is reached. This may take 2-6 weeks.
  f) In adolescents, long-acting or intermediate acting insulin may be added at a dose of 0.5 u/kg at bed-time. 441 (Level III)
Algorithm 9: Approach to Initial and Subsequent Treatment of Adolescents with T2DM

*Adopted from ISPAD Clinical Practice Consensus Guidelines 2014 Compendium, Pediatric Diabetes 2014:15 (Suppl. 20):26-4*
• Goal of treatment is to achieve A1c <6.5%. \(^{442}\) (Level III)

• The following monitoring is essential to avoid long term complications: \(^{442}\) (Level III)
  a) At diagnosis and annually thereafter:
    i. Test for microalbuminuria or macroalbuminuria
    ii. Examination for retinopathy
    iii. Test for dyslipidaemia
    iv. Evaluation for non-alcoholic fatty liver disease (NAFLD)
  
  b) At every clinic visit:
   i. Weight and height
   ii. BP (hypertensive if BP >95\textsuperscript{th} percentile for age, sex and height percentile) at every visit.
   Online instructions are available at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf
   iii. Inquiry about puberty, menstrual irregularities and obstructive sleep apnoea
   iv. Psychosocial wellbeing (depression, eating disorder)

---

**Recommendations: Diabetes in Adolescents**

1. For those at risk of developing diabetes, screening should be initiated at 10 years of age or at onset of puberty if puberty occurs at a younger age, and repeated every 2 years. [Grade C]
2. A glucose load of 1.75 g/kg body weight (maximum of 75 g) for OGTT is used. [Grade C]
3. Treatment of T2DM in adolescents follow the same rationale as does treatment in adults. [Grade C]

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### 6.4 Diabetes in the Elderly

• Diabetes is more common in the elderly (>60 years old). The prevalence of T2DM in patients between the ages of 60-64, 65-69 and 70-74 are 36.2\%, 36.6\% and 30.3\%, respectively. \(^{1}\) (Level II-2)

• The elderly with diabetes is a very heterogeneous group comprising of active individuals with little comorbidity and complications on one end of the spectrum to frail individuals with multiple serious comorbidities and disabling complications on the other.

• There are those who have recently been diagnosed with diabetes and many who have long standing diabetes with multiple complications.

• They are at an increase rate of concomitant illnesses e.g. hypertension, renal impairment, ischaemic heart disease and functional disabilities vis increased risk of falls.

• Elderly with diabetes also have a higher incidence of age-related problems which may be exacerbated by diabetes for example cognitive impairment, incontinence and polypharmacy.

• The life expectancy within this elderly diabetic population is highly variable.

**Management**

• In the elderly with T2DM and established complications, intensive control reduces only the risk of microvascular events but not macrovascular events or mortality. \(^{43,47,443}\) (Level I)

• However, better glycaemic control is associated with less disability and better functioning. \(^{444,445}\) (Level II-2)

• Postprandial glucose values have been shown to be a better predictor of outcome in elderly patients compared to A1c or preprandial glucose values. \(^{446}\) (Level I)
Greater variability of glucose values is associated with poorer cognition despite equivalent glycaemic control. This is not surprising given that hypoglycaemic episodes, are more common in the elderly. Cognitive dysfunction and frailty increases the risk of hypoglycaemia and this causes further impairment of cognitive dysfunction and exacerbate frailty.

Thus, the decision of how tight the glycaemic control is less dependent on the chronological age but more on the degree of frailty and overall life expectancy of each individual.

The principle of the use of various OADs is similar in the elderly as in younger patients. Sulphonylureas should be used with caution because the risk of severe or fatal hypoglycaemia increases exponentially with age and is higher with glibenclamide than gliclazide and glimepiride.

Similar to OAD, the use of insulin in the elderly is associated with increased risk of hypoglycaemia, therefore every effort should be made to minimise the risk.

Other comorbidities should also be treated to goal.

Table 42: Treatment Goals for Glycaemia, Blood Pressure, and Dyslipidaemia in Elderly with Diabetes

<table>
<thead>
<tr>
<th>Patient Characteristics / Health Status</th>
<th>Rationale</th>
<th>Reasonable A1c Goal</th>
<th>Blood Pressure (mm Hg)</th>
<th>Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few coexisting chronic illnesses, intact cognitive and functional status)</td>
<td>Longer life expectancy</td>
<td>≤7.0%</td>
<td>&lt;135/75</td>
<td>LDL-C: &lt;2.6 mmol/L, or &lt;1.8 mmol/L (overt CVD)</td>
</tr>
<tr>
<td>Complex/intermediate (multiple coexisting chronic illnesses* or mild-to moderate cognitive and functional impairment)</td>
<td>Intermediate life expectancy, high treatment burden, hypoglycaemia vulnerability, fall risk</td>
<td>&lt;8.0%</td>
<td>&lt;140/90</td>
<td>Non-HDL-C: &lt;3.4 mmol/L HDL-C: &gt;1.0 mmol/L (male) &gt;1.2 mmol/L (female) TG: &lt;1.7 mmol/L</td>
</tr>
<tr>
<td>Very complex/poor health (long-term care or end stage chronic illnesses** or moderate-to-severe cognitive and functional impairment)</td>
<td>Limited life expectancy makes benefit uncertain</td>
<td>&lt;8.5%</td>
<td>&lt;150/90</td>
<td>Individualised</td>
</tr>
</tbody>
</table>

Modified from American Diabetes Association—Standards of Medical Care in Diabetes—2015.  

1 A lower A1c goal may be set for an individual if achievable without recurrent or severe hypoglycaemia or undue treatment burden.  

* Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include debilitating arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction and stroke.  

** The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, which significantly reduce life expectancy.
6.5 Diabetes in Ramadan

- Fasting during Ramadan is obligatory for all healthy adult Muslims.

- Fasting in certain individuals with diabetes may be associated with adverse outcomes; hence they are not obliged to fast.

- However, many diabetic patients choose to fast as shown in the Epidemiology of Diabetes and Ramadan (EPIDIAR) study, 453 (Level II-2) despite a clear instruction from the Quran on individuals who are exempted from fasting. These include individuals with chronic diseases such as diabetes mellitus. (Surah Al Baqarah Verse 184-185).

- Management of Muslim T2DM patients during Ramadan continues to be a challenge for health care professionals. 454 (Level II-2)

- There are several potential risks associated with fasting in Ramadan namely hypoglycaemia, hyperglycaemia/DKA and dehydration.

- It is important to categorise patients who intend to fast based on risk stratification as listed in APPENDIX 8. Those in high- and very high-risk categories should abstain from fasting. 454 (Level II-2)

Preparation Prior to Ramadan

- A pre-Ramadan medical assessment of general well-being, glycaemic control, comorbidities and complications should be performed to categorise the patient in terms of the risks from fasting as well as to optimise their management.

- Patients and care-givers should receive education concerning self-care on the following: 455-457 (Level III)
  a) Risks from fasting:
     i. Hypoglycaemia – symptoms and signs, response
     ii. Hyperglycaemia – symptoms and signs, response
     iii. Dehydration
  b) Blood glucose monitoring – during fasting and non-fasting hours
  c) When to stop the fast
  d) Adequate fluid intake
  e) Meal planning and food choices
  f) Physical activity – timing and intensity
  g) Medication administration – timing and dosing
  h) Management of acute complications

- Patients must immediately end their fast when:
  a) Blood glucose <3.3 mmol/L at any time during the fast. 458 (Level II-2)

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Recommendations: Diabetes in Elderly

1. Postprandial glucose values are a better outcome predictor compared to A1c or preprandial glucose values. [Grade C]

2. The glycaemic targets depend on the degree of frailty and overall life expectancy of each individual, rather than chronological age. [Grade C]

3. Other comorbidities should be treated to goal. [Grade C]
b) Blood glucose <3.9 mmol/L in the first few hours of fasting (especially if the patient is taking sulfonylureas, meglitinides, or insulin). 457,459 (Level II-2)

c) Blood glucose >16.7 mmol/L. 458 (Level II-2)

d) Experience symptoms of hypoglycaemia (patients without SMBG).

e) Symptoms suggestive of severe dehydration such as syncope and confusion.

Adjustment of the Diet Protocol for Ramadan Fasting 460 (Level III)

- Never skip *Sahur* (pre-dawn meal). *Sahur* should consist of a balanced meal with adequate carbohydrate taken as late as possible just before *Imsak* (dawn) to avoid unnecessarily prolonged fasting.

- Do not delay the breaking of fast at sunset (*Iftar*). Limit intake of high-sugar foods. However, 1–2 *kurma* (dates) at the start of *Iftar* following the practice of the Prophet (*Sunnah*) may be taken as part of carbohydrate exchange. The main meal is encouraged after the performance of *Maghrib* prayers.

- Supper after *Tarawih* (*supererogatory prayers*) can be considered as a pre-bed snack during non-fasting month.

- Limit intake of salty foods to reduce risk of dehydration.

- Sufficient fluid must be taken to replenish fluid loss during the day. Aim for 8 glasses of fluid a day.

Physical Activity

- Physical activities and exercise need to be adjusted during Ramadan. The following are recommended: 467,461 (Level III)

  a) Light and moderate intensity exercise on a regular basis.

  b) Avoid rigorous exercise during daytime because of the risk of hypoglycaemia.

  c) The timing of exercise is preferably performed 1-2 hours after the break of fast.

  d) Performance of *Tarawih* prayers is a form of physical activity.

Anti-diabetic Agents for Patient with T2DM Who Fast During Ramadan

- Anti-diabetic therapies should be individualised during fasting. 454 (Level II-2)

Oral Anti-diabetic Agents

- In principle, the non-fasting morning dose should be taken during *Iftar*, and the non-fasting evening dose should be taken during *Sahur*. 

83
### Table 43: Adjustment of Oral Anti-diabetic Agents During Fasting in Ramadan 462 (Level III)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Iftar</th>
<th>Sahur</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGI</td>
<td>No changes</td>
<td>No changes</td>
</tr>
<tr>
<td>Biguanides</td>
<td>No changes</td>
<td>No changes</td>
</tr>
<tr>
<td>(metformin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Switch timing to Iftar</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>No changes</td>
<td>No changes</td>
</tr>
<tr>
<td>SUs</td>
<td>No changes</td>
<td>Glibenclamide: Reduce/omit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gliclazide: Reduce/omit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glimepiride: Switch timing to Iftar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gliclazide MR: Switch timing to Iftar</td>
</tr>
<tr>
<td>SGLT2i*</td>
<td>Switch timing to Iftar</td>
<td></td>
</tr>
<tr>
<td>TZDs</td>
<td>No changes</td>
<td></td>
</tr>
</tbody>
</table>

AGI = alpha-glucosidase inhibitors; DPP-4i = dipeptidyl peptidase-4 inhibitors; SUs = sulphonylureas; SGLT2i = sodium-glucose cotransporter 2 inhibitors; TZDs = thiazolidinediones; *Based on the expert opinion of the committee.

### Injectable Anti-diabetic Agents

**Glucagon-like peptide-1 receptor agonists (GLP-1 RA)**

### Table 44: Adjustment of GLP-1 RA During Fasting in Ramadan:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Iftar</th>
<th>Sahur</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Switch timing to Iftar</td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 RA = glucagon-like peptide-1 receptor agonists

### Insulin Therapy During Ramadan

Individualised adjustments of insulin dose and timing will need to be implemented when fasting during Ramadan. Those who are prone to develop hypoglycaemia, insulin analogues may be used. 454 (Level II-2)
Table 45: Insulin Adjustments During Ramadan

<table>
<thead>
<tr>
<th>Insulin Regimen</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin only</td>
<td>Basal Insulin to be taken at bedtime or after Iftar meals. May need dose reduction if there is a risk of daytime hypoglycaemia.</td>
</tr>
<tr>
<td>Premixed insulin once daily</td>
<td>Inject usual dose at Iftar.</td>
</tr>
<tr>
<td>Premixed insulin twice daily</td>
<td>Reverse doses – Morning dose given at Iftar and evening dose at Sahur. Insulin dose at Sahur reduced by 20-50% to prevent daytime hypoglycaemia. or Change to short/rapid acting.</td>
</tr>
<tr>
<td>Basal bolus insulin</td>
<td>Taken at bedtime or any time after Iftar meals. May require a dose reduction if there is daytime hypoglycaemia. Sahur – Usual pre-Ramadan breakfast or lunch dose. May require a dose reduction to avoid daytime hypoglycaemia. Lunch – Omit. Iftar – Usual pre-Ramadan dinner dose. May require dose increment.</td>
</tr>
<tr>
<td>Insulin Pump</td>
<td><strong>Basal insulin rate</strong>: May require reduction of up to 25%. <strong>Prandial bolus</strong>: According to individualised insulin-to-carbohydrate ratio (ICR).</td>
</tr>
</tbody>
</table>

**Recommendations: Diabetes in Ramadan**

1. A pre-Ramadan medical assessment of general well-being, glycaemic control, comorbidities and complications should be performed to categorise the patient’s risks from fasting as well as to optimise their management. [Grade C]
2. Patients and care-givers should receive education concerning self-care on risks of hypoglycaemia, hyperglycaemia and dehydration. [Grade C]
3. Anti-diabetic therapies should be individualised during fasting. [Grade C]
SECTION 7  PREVENTION OF TYPE 2 DIABETES MELLITUS

7.1 For People At Risk

- There are many risk factors that predispose an individual or population to developing glucose intolerance and eventually diabetes.

- Those at risk include individuals with:
  a) a family history of diabetes (1st degree relatives).
  b) gestational diabetes mellitus.
  c) hypertension.
  d) vascular disease.
  e) dyslipidaemia.
  f) obesity or overweight with central obesity.
  g) polycystic ovarian syndrome.

- There is ample evidence that lifestyle related changes, in particular, weight gain and sedentary lifestyle are the main factors influencing the explosion of diabetes, a result of the rapid urbanisation of our society. As diabetes is an endpoint in the glucose tolerance continuum, it is possible to halt this slide from normal to IGT and subsequently T2DM.

7.2 Pre-diabetes

- Patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and/or A1c 5.6–6.2% are considered as having pre-diabetes.

- Pre-diabetes increases the risk of progression to T2DM. In addition, patients with pre-diabetes have a higher risk of cardiovascular disease.

- Progression to diabetes in patients with pre-diabetes can be delayed.

- Interventions proven to reduce the conversion of IFG/IGT to T2DM:
  a) Diet and moderate intensity physical activity (which result in a modest weight loss of 5-7% of body weight). 20,45,467-469 (Level I) These remain the mainstay of therapy.
  b) In addition to lifestyle intervention, metformin can be considered for those at very high risk (combined IFG & IGT, IGT + obesity (BMI >35 kg/m^2), IGT + < 60 years old, previous history of GDM or for those who failed lifestyle therapy after 6 months. 45,470,471 (Level I)
  c) Other pharmacological interventions that have been shown to delay the onset of T2DM are acarbose, orlistat and rosiglitazone. 472,473 (Level I) However, their use for prevention of T2DM has not been endorsed.

- Metformin is the only drug that has received endorsement by other national guidelines for the prevention of T2DM. 4,474 (Level III)

- Lifestyle intervention programmes have greater efficacy 20 (Level I) than pharmacological intervention and are practical and cost effective, making its implementation possible in any primary healthcare setting. 20,212,467,468,470 (Level II-3)

- Behavioural and lifestyle modification have shown long-term effects on prevention of diabetes beyond the period of active intervention. 471,475-477 (Level II-2)

- Annual assessment / monitoring for glucose tolerance status is recommended. 4 (Level III)
• Screening and appropriate management of other modifiable cardiovascular risk factors is suggested. 4 (Level III)

**Recommendations: Prevention of Type 2 Diabetes Mellitus**

1. In patients with IGT, a structured programme of lifestyle modification that includes modest weight loss (5–7% of body weight) and regular moderate-intensity physical activity (at least 150 minutes a week) has been shown to reduce the risk of progression to T2DM. *[Grade A]*

2. Use of pharmacological intervention such as metformin can be considered in those who failed lifestyle intervention (after 6 months). *[Grade C]*
SECTION 8  UNPROVEN THERAPIES IN DIABETES MELLITUS

8.1 Alternative Therapies

- Alternative medicine is any therapy that has not been scientifically tested, defined as having “rigorous evidence of safety and efficacy, as required by the Food and Drug Administration (FDA) for the approval of drugs.” 478 (Level III)

- A variety of products claiming to lower blood glucose levels or prevent and treat diabetes complications and comorbidities are flooding the marketplace. 479-482 (Level III) For example, nutritional supplements are popular with people looking for an alternative treatment.

- The 2015 American Diabetes Association guidelines state there is no sufficient evidence to recommend the daily use of supplements such as chromium, magnesium, vitamin D, cinnamon or herbs/supplements. 4 (Level III) There is no benefit unless the patient lacks that nutrient or mineral.

- Many patients with diabetes are hesitant to tell their healthcare providers of their complementary therapy use. 479 (Level III) These may contain harmful ingredients or may be otherwise unsafe, or may improperly be marketed as over-the-counter (OTC) products when they should be marketed as prescription products.

- The success of some alternative treatments can be difficult to measure. Furthermore, they may result in an additional harm to the patients if the treatment for diabetes is delayed or discontinued. 480 (Level III)

- Unproven therapies tend to share the following features: 483 (Level III)
  a) They tend to be produced and promoted in isolation from established scientific facilities and associations, and their developers usually do not have strong clinical or scientific qualifications.
  b) The rationales for these therapies often contain misapplication of data from the scientific literature.
  c) Proponents often overstated or give unrealistic claims about these therapies.
  d) These therapies often have possible financial profit to those who have developed, promoted, or approved them.
  e) They are generally promoted outside regular channels of scientific and clinical interactions and the details of the therapies are usually unclear.
  f) Their proponents sometimes deter or decline discussion with or assessment by reputable clinicians or scientists.
  g) Their developers and promoters often claim that a medical or scientific “plot” has been convened to oppose them.

- Healthcare providers are uniquely positioned to encourage patients to discuss openly about their use of alternative products. Patients with diabetes must be educated about which of such therapies may be of some benefit and those with absolutely no proven value.

- It is very important to inform patients not to replace conventional medical therapy for diabetes with an unproven alternative therapy. Patients need to be cautioned on the potential side effects, drug interactions, and lack of product standardisation, in addition to the increased costs that patients may incur when they use ineffective therapies or delay treatment with proven therapeutic agents.
• One of the issues with the use of alternative therapies is the increasing incidence of kidney and liver failure following the use of such alternative therapies. \( ^{479} \) (Level III) Medicines for diabetes and other health conditions may need to be adjusted if a person is also using an alternative treatment.

• Healthcare professionals and consumers are encouraged to report any adverse events related to products intended to treat or cure diabetes to the Malaysian Adverse Drug Reaction Advisory Committee (MADRAC) at https://www.bpfk.gov.my. \( ^{484} \) (Level III)

8.2 Traditional and Complementary Medicine

• Traditional and complementary medicines (TCM) are widely used by diabetic patients. Studies have shown that in Malaysia, about 70% of patients with T2DM were on complementary medicines. \( ^{485,486} \) (Level II-2) It is important to be aware of the potential side effects and drug interactions of these medicines though some may be showing reduction in glucose level.

• Most of the TCMs in this country were approved as a supplement, and there is no randomised clinical trials performed with these products. Most studies were done in animal models and trials in human tend to be of shorter duration and involve smaller sample sizes.

• A number of TCMs have been studied to evaluate the impact on glycaemic control, insulin secretion and also insulin resistance. Most studies showed conflicting results between them. \( ^{487-496} \) (Level II-3)

• Healthcare providers should always ask about the use of complementary medicines in their patients as it is commonly taken together with conventional anti-diabetic agents. Complementary medicines should not be recommended to patients with T2DM.

**Recommendations: Unproven Therapies in Diabetes Mellitus**

1. Healthcare providers should inquire about the use of alternative therapies and TCMs in diabetic patients. [Grade C]
2. Alternative therapies and TCMs are not recommended for glycaemic control for patients with diabetes as there are insufficient evidence regarding efficacy and safety [Grade C].
SECTION 9 IMPLEMENTING THE GUIDELINES

This section provides some insight into the following:

- Potential barriers in applying the recommendations
- Necessary steps to ensure effective compliance to the guidelines
- Implementation strategies and resources implications in applying the recommendations
- Proposed clinical audit indicators for quality management that will aid in the implementation of the guidelines.

Implementation of this CPG is an important component of clinical governance. It caters to all medical and health institutions including medical centres, hospitals and health clinics both in the public and private sectors. In doing so every attempt should be made to take both the economic and non-economic considerations into account. Mechanisms should also be in place to review the existing healthcare system in accordance with the CPG recommendations. Any differences should be assessed and addressed accordingly.

9.1 Potential Barriers in Applying the Recommendations

We have identified three main groups of barriers in applying the recommendations of the CPG in the local context:

i. Patient factors
   - Lack of awareness and knowledge of T2DM and the complications related to the disease.
   - Unfounded attitudes, beliefs and perceptions regarding T2DM, its complications and management.
   - Misplaced priorities and expectations regarding T2DM and its management
   - Lack of financial resources to have access to a wide range of therapeutic options and to monitor treatment
   - Complexity of existing treatment regimes and schedules

ii. Healthcare professional factors
   - Limited knowledge and experience in managing T2DM
   - Lack of manpower such as trained diabetes educators.
   - “Clinical inertia” defined as failure to intensify treatment of a patient who is not at their evidence-based targets
   - Inability to reconcile patient preferences with guideline recommendations
   - Lack of utilisation of available resources
   - Service burden and increased patient load
   - Disproportionate financial remuneration and rewards
   - Lack of a well-defined career pathway and professional advancement (diabetes educators)

iii. Health services factors
   - Inequality in the distribution of manpower, resources and facilities
   - Limited resources and facilities
   - Budgetary and economic constraints
   - Long waiting list for specialist consultation
   - Inadequate prioritisation of available manpower and resources
9.2 Necessary Steps To Ensure Effective Compliance to the Guidelines

Important programmes that should be considered when implementing this CPG include:

• Establishment of an effective screening programme that utilises FPG, modified OGTT and A1c at various medical and health centres.
• Ensuring laboratory assays such as A1c adhere to good laboratory practice and participate in quality control monitoring.
• Availability of facilities and resources to monitor treatment and to screen for complications such as A1c testing, 12-lead ECG, monofilament, urine dipstick, retinal camera etc.
• Adequate training and privileging of health care providers in the overall management of T2DM.
• Availability of trained diabetes educators in public-run health clinics.
• Increasing the availability of various classes of anti-diabetic agents in public-run health facilities.
• Consolidating and expanding the current National Diabetes Registry thus ensuring a wider coverage involving both the public and private sectors.
• Effective and efficient referral system for complicated cases of T2DM.

With the availability of this national evidence-based CPG, the current nation-wide screening and management programme will be strengthened to prevent serious complications among patients with T2DM.

9.3 Implementation Strategies and Implications to Resources in Applying the Recommendations

The implementation of the CPG will be facilitated by the existing CPG Training Module which was produced by the Ministry Of Health, Academy of Medicine Malaysia, Malaysian Endocrine & Metabolic Society and Diabetes Malaysia. The module was implemented since 2009 primarily to help in the training of medical specialists, family medicine specialists, general practitioners, medical officers, allied health professionals, diabetes educators and nurses in the holistic management of T2DM. The Development Group will ensure that the contents of this training module will incorporate the recommendations of the current CPG.

The materials for the training module would include the following:

a) The complete guideline in a booklet form
b) Quick reference guidelines for both health care practitioners and patients
   i. Diagnosis & Management of T2DM
   ii. Management of Diabetic Emergencies
   iii. Special populations such as pregnant women etc
c) Poster-sized important algorithms of the CPG
d) Training Slides based on the various sections of the CPG
e) Short training videos on important practical procedures such SBGM, insulin injection techniques, treatment of hypoglycaemia.

Training workshops will be planned at various levels including federal, state and district. The peninsular will be divided into 4 geographical zones while Sabah and Sarawak will constitute a zone. A national training workshop will be followed by similar workshops at the level of the 5 zones before the exercises are repeated at the states and main districts. These training workshops will be conducted by members of the development committee and various experts who are trained in the implementation of the CPG.

Funding will be solicited from MOH, NGOs such as MEMS, Diabetes Malaysia (DM), Malaysian Family Medicine Specialist Association among others and the relevant pharmaceutical industry.
Data on the following parameters:

a) success of various screening programmes,
b) proportion of patients that are screened for complications,
c) proportion of patients meeting various targets,
d) proportion of patients that received education and
e) percentage of facilities managing diabetes with trained personnel will be analysed and reviewed.

Based on the above findings, recommendations with regards to dissemination of funds, allocation of resource, training and distribution of manpower will be restructured to ensure the smooth implementation of the guidelines at every level of T2DM patient care. In essence, financial and staffing allocation should be appropriately distributed to individual hospitals, health clinics and facilities to achieve adequate access to screening programmes and resources to treatment.

9.4 Guide to Key Performance Indices (KPI)

In view of the high prevalence of T2DM \(^1\) (Level II-2) and the poor diabetic control \(^2\) (Level II-2), the development group proposes the following 5 main clinical audit indicators for quality assessment as part of ensuring the ongoing compliance to the recommendations in the CPG:

\[
\text{Percentage of patients screened for T2DM} = \frac{\text{Number of patients screened for T2DM}}{\text{Total number of patients attending the facility}} \times 100\% 
\]

(Proposed Target : 50%)

\[
\text{Percentage of T2DM patients achieving targets} = \frac{\text{Number of patients achieving targets}}{\text{Total number of T2DM patients attending the facility}} \times 100\% 
\]

(Proposed Target : 30% for primary care & 20% for tertiary care)

\[
\text{Percentage of patients screened for complications} = \frac{\text{Number of patients screened for complications}}{\text{Total number of T2DM patients attending the facility}} \times 100\% 
\]

(Proposed Target: 75% for primary care & 90% for tertiary care)

\[
\text{Percentage of T2DM patients receiving education} = \frac{\text{Number of patients receiving education}}{\text{Total number of T2DM patients attending the facility}} \times 100\% 
\]

(Proposed Target: 75% for primary care & 90% for tertiary care)

\[
\text{Percentage of facility with diabetes educator} = \frac{\text{Number of facility with diabetes educator}}{\text{Total number of facilities managing T2DM}} \times 100\% 
\]

(Proposed Target: 50% for primary care)

The targets are proposed based on existing data taking into account the practicality of the recommendations and the reality of the current available resources and facilities.
REFERENCES


56. The Look AHEAD Research Group. Reduction in Weight and Cardiovascular Disease Risk Factors in Individuals with Type 2 Diabetes: One-year results of the Look AHEAD trial. *Diabetes Care.*


176. Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation (IDF) Western Pacific Region. Type 2 Diabetes Practical Targets and Treatments. 4 ed. Melbourne, Australia: International Diabetes Institute (IDI); 2005.


188. Malaysian Society of Hypertension.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chico A, Vidal-Rios P, Subira M, Novials A.</td>
<td>The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemas in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control.</td>
<td><em>Diabetes Care.</em> 2003;26(4):1153-1157.</td>
</tr>
</tbody>
</table>

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448. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment
approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010;340:b5444.


### APPENDIX 1: Carbohydrate Content of Common Malaysian Foods

<table>
<thead>
<tr>
<th>Foods</th>
<th>Serving</th>
<th>Calories (kcal)</th>
<th>CHO Content (g)</th>
<th>Approx. CHO Exchanges*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooked rice</td>
<td>1 bowl (159 g)</td>
<td>207</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Roti canai</td>
<td>1 piece (95 g)</td>
<td>301</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Chappati</td>
<td>1 piece (100 g)</td>
<td>300</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>Curry mee</td>
<td>1 bowl (450 g)</td>
<td>549</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>Fried noodles (mee/meehoon)</td>
<td>1 plate (30 g)</td>
<td>281</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Bread (white/wholemeal)</td>
<td>1 slice (30 g)</td>
<td>70</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Biscuits, unsweetened</td>
<td>2 pieces (18 g)</td>
<td>80</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Curry puff</td>
<td>1 piece (40 g)</td>
<td>128</td>
<td>17</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Potato</td>
<td>1 medium (90 g)</td>
<td>90</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Dhal (raw)</td>
<td>½ cup (98 g)</td>
<td>98</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>Full cream milk</td>
<td>1 cup (250 ml)</td>
<td>187</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Low fat milk</td>
<td>1 cup (250 ml)</td>
<td>131</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Skim milk powder</td>
<td>4 tablespoon (28 g)</td>
<td>100</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Condensed milk, sweetened</td>
<td>2 tablespoon (40 g)</td>
<td>126</td>
<td>21</td>
<td>1.5</td>
</tr>
<tr>
<td>Apple/orange</td>
<td>1 medium (114 g)</td>
<td>40</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Banana (pisang mas)</td>
<td>1 small (50 g)</td>
<td>40</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Star fruit</td>
<td>1 medium (260 g)</td>
<td>56</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Durian local</td>
<td>5 small seeds (189 g)</td>
<td>64</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Langsat/grapes/longan</td>
<td>8 small (233 g)</td>
<td>52</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Guava</td>
<td>½ fruit (100 g)</td>
<td>50</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Watermelon/papaya/ pineapple</td>
<td>1 slice (160 g)</td>
<td>56</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Mango</td>
<td>1 small (100 g)</td>
<td>50</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

* 1 CHO Food Exchange = 15 g; CHO = carbohydrate

## APPENDIX 2: Food Groups and Exchange List

### Cereals, Grain Products and Starchy Vegetables

(Each item contains 15 g carbohydrate, 2 g protein, 0.5 g fat and 75 calories)

<table>
<thead>
<tr>
<th>Cereals, Grain &amp; Bread</th>
<th>Exchange with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice, white unpolished (cooked)</td>
<td>½ cup or 1/3 Chinese rice bowl</td>
</tr>
<tr>
<td>Can be exchanged for</td>
<td></td>
</tr>
<tr>
<td>Rice porridge</td>
<td>1 cup</td>
</tr>
<tr>
<td>Kway teow</td>
<td></td>
</tr>
<tr>
<td>Mee hoon</td>
<td>½ cup or 1/3 Chinese rice bowl</td>
</tr>
<tr>
<td>Spaghetti</td>
<td></td>
</tr>
<tr>
<td>Macaroni</td>
<td></td>
</tr>
<tr>
<td>Mee, wet</td>
<td>1/3 cup</td>
</tr>
<tr>
<td>Idli</td>
<td>1 piece (60 g)</td>
</tr>
<tr>
<td>Putu mayam</td>
<td>1 piece (40 g)</td>
</tr>
<tr>
<td>Thosai, diameter 20 cm</td>
<td>½ piece</td>
</tr>
<tr>
<td>Chappati, diameter 20 cm</td>
<td>1/3 piece</td>
</tr>
<tr>
<td>Bread (wholemeal, high fibre, white/brown)</td>
<td>1 slice (30 g)</td>
</tr>
<tr>
<td>Plain roll</td>
<td>1 small (30 g)</td>
</tr>
<tr>
<td>Burger bun</td>
<td>½ piece</td>
</tr>
<tr>
<td>Pita bread, diameter 6 inches</td>
<td>½ piece</td>
</tr>
<tr>
<td>Oatmeal, cooked</td>
<td>¼ cup</td>
</tr>
<tr>
<td>Oats, uncooked</td>
<td>3 rounded tablespoons</td>
</tr>
<tr>
<td>Muesli</td>
<td>¼ cup</td>
</tr>
<tr>
<td>Flour (wheat, rice, atta)</td>
<td>3 rounded tablespoons</td>
</tr>
<tr>
<td>Biscuits (plain, unsweetened) e.g. cream crackers, Ryvita</td>
<td>3 pieces</td>
</tr>
<tr>
<td>Small thin, salted biscuits (4.5 x 4.5 cm)</td>
<td>6 pieces</td>
</tr>
</tbody>
</table>

### Starchy Vegetables

*Baked beans, canned | 1/3 cup |
*Lentils | 1/3 cup |

(*Contains more protein than other foods in the list i.e. 5 g/serve)

<table>
<thead>
<tr>
<th>Starchy Vegetables</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn kernel (fresh/canned)</td>
<td>½ cup</td>
</tr>
<tr>
<td>Peas (fresh/canned)</td>
<td>½ cup</td>
</tr>
<tr>
<td>Sweet potato</td>
<td></td>
</tr>
<tr>
<td>Tapioca</td>
<td>½ cup (45 g)</td>
</tr>
<tr>
<td>Yam</td>
<td></td>
</tr>
<tr>
<td>Breadfruit (sukun)</td>
<td>1 slice (75 g)</td>
</tr>
<tr>
<td>Pumpkin</td>
<td>1 cup (100 g)</td>
</tr>
<tr>
<td>Corn on the cob, 6 cm length</td>
<td>1 small</td>
</tr>
<tr>
<td>Potato</td>
<td>1 small (75 g)</td>
</tr>
<tr>
<td>Potato, mashed</td>
<td>½ cup</td>
</tr>
<tr>
<td>Waterchestnut</td>
<td>4 pieces</td>
</tr>
</tbody>
</table>

- 1 cup = 200 mL in volume = ¾ Chinese rice bowl (11.2 cm in diameter x 3.7 cm deep)
- Tablespoon refers to dessert spoon level (equivalent to 2 teaspoons)

Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013.57 (Level III)
### APPENDIX 2: Food Groups and Exchange List (cont.)

<table>
<thead>
<tr>
<th>Fruits</th>
<th>(Each item contains 15 g carbohydrate and 60 calories)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange</td>
<td>1 medium</td>
</tr>
<tr>
<td>Can be exchanged for</td>
<td></td>
</tr>
<tr>
<td>Banana</td>
<td>1 small (60 g)</td>
</tr>
<tr>
<td>Apple</td>
<td></td>
</tr>
<tr>
<td>Custard apple (buah nona)</td>
<td></td>
</tr>
<tr>
<td>Star fruit</td>
<td></td>
</tr>
<tr>
<td>Pear</td>
<td>1 medium</td>
</tr>
<tr>
<td>Peach</td>
<td></td>
</tr>
<tr>
<td>Persimmon</td>
<td></td>
</tr>
<tr>
<td>Sapodilla (ciku)</td>
<td></td>
</tr>
<tr>
<td>Kiwi</td>
<td></td>
</tr>
<tr>
<td>Hog plum (kedondong)</td>
<td>6 whole</td>
</tr>
<tr>
<td>Mangosteen</td>
<td>2 small</td>
</tr>
<tr>
<td>Plum</td>
<td>2 small</td>
</tr>
<tr>
<td>Duku langsat</td>
<td></td>
</tr>
<tr>
<td>Grapes</td>
<td></td>
</tr>
<tr>
<td>Langsat</td>
<td>8 pieces</td>
</tr>
<tr>
<td>Longan</td>
<td></td>
</tr>
<tr>
<td>Water apple (jambu air), small</td>
<td></td>
</tr>
<tr>
<td>Lychee</td>
<td>5 whole</td>
</tr>
<tr>
<td>Rambutan</td>
<td>5 whole</td>
</tr>
<tr>
<td>Pomelo</td>
<td>5 slices</td>
</tr>
<tr>
<td>Papaya</td>
<td></td>
</tr>
<tr>
<td>Pineapple</td>
<td>1 slice</td>
</tr>
<tr>
<td>Watermelon</td>
<td></td>
</tr>
<tr>
<td>Soursop (durian belanda)</td>
<td></td>
</tr>
<tr>
<td>Guava</td>
<td>½ fruit</td>
</tr>
<tr>
<td>Cempedak</td>
<td>4 pieces</td>
</tr>
<tr>
<td>Jack fruit (nangka)</td>
<td>4 pieces</td>
</tr>
<tr>
<td>Prunes</td>
<td>3 pieces</td>
</tr>
<tr>
<td>Dates (kurma), dries</td>
<td>2 pieces</td>
</tr>
<tr>
<td>Raisin</td>
<td>20 g</td>
</tr>
<tr>
<td>Durian</td>
<td>2 medium seeds</td>
</tr>
<tr>
<td>Mango</td>
<td>½ small</td>
</tr>
</tbody>
</table>

* Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. (Level III)
## APPENDIX 2: Food Groups and Exchange List (cont.)

### Lean Meat, Fish and Meat Substitutes
(Each serving of meat and substitutes contain 7 g of protein. These foods contain varying amounts of fat and energy, but negligible carbohydrate)

<table>
<thead>
<tr>
<th></th>
<th>CHO (g)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Energy (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean meat/Meat substitutes</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>65</td>
</tr>
<tr>
<td>Fish/Shellfish</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td>35</td>
</tr>
</tbody>
</table>

#### Lean Meat

- Chicken (raw, without skin) ½ drumstick

**Can be exchanged for**

- Lean meat (all varieties) 1 small serve (40 g)
- Poultry (young) 40 g raw/30 g cooked
- Egg (hen) 1 medium
- Soya bean curd (taukua) ½ piece (60 g)
- Soya bean curd (soft, tauhoo) ¾ piece (90 g)
- Soya bean curd, sheet (fucok) 1 ½ sheets (30 g)
- Tempeh 1 piece (45 g)
- Cheese, cheddar 2 thin slices (30 g)
- Cottage cheese ¼ small cup

#### Fish / Shellfish

- Fish (e.g. ikan kembong, selar) ½ piece (40 g)
- Fish cutlet ¼ piece (40 g)
- Squid 1 medium (40 g)
- Crab meat ¼ cup
- Lobster meat
- Prawn meat
- Cockles 20 small
- Prawn 6 medium

*Beans and lentils are good sources of protein but they also contain carbohydrate.

### Milk
(Milk contains varying amount of carbohydrate, fat and protein depending on the types)

<table>
<thead>
<tr>
<th></th>
<th>CHO (g)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Energy (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skimmed (1% fat)</td>
<td>15</td>
<td>8</td>
<td>Trace</td>
<td>90</td>
</tr>
<tr>
<td>Low fat (2% fat)</td>
<td>12</td>
<td>8</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>Full cream</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>150</td>
</tr>
</tbody>
</table>

#### Milk
- Fresh cow’s milk
- UHT fresh milk 1 cup (240 ml)
- Powdered milk (skim, full cream) 4 rounded tablespoons or 1/3 cup
- Yogurt (plain/low fat) ⅜ cup
- Evaporated (unsweetened) ⅝ cup

* Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. 57 (Level III)
## APPENDIX 2: Food Groups and Exchange List (cont.)

<table>
<thead>
<tr>
<th>Fat</th>
<th>Can be exchanged for</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oil (all types)</strong></td>
<td>1 level teaspoon (5 g)</td>
</tr>
<tr>
<td><strong>Butter, margarine</strong></td>
<td>1 level teaspoon</td>
</tr>
<tr>
<td><strong>Mayonnaise</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Shortening, lard</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Peanut butter (smooth or crunchy)</strong></td>
<td>2 level teaspoons</td>
</tr>
<tr>
<td><strong>Cream, unwhipped (heavy)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cream cheese</strong></td>
<td>1 level tablespoon</td>
</tr>
<tr>
<td><strong>Salad dressing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cream, unwhipped (light)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Coconut, shredded</strong></td>
<td>2 level tablespoons</td>
</tr>
<tr>
<td><strong>Coconut milk (santan)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non dairy creamer, powder</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Almond</strong></td>
<td>6 whole</td>
</tr>
<tr>
<td><strong>Cashew nut</strong></td>
<td>6 whole</td>
</tr>
<tr>
<td><strong>Walnut</strong></td>
<td>1 whole</td>
</tr>
<tr>
<td><strong>Peanut</strong></td>
<td>20 small</td>
</tr>
<tr>
<td><strong>Sesame seed</strong></td>
<td>1 level tablespoon</td>
</tr>
<tr>
<td><strong>Watermelon seed (kuachi) with shell</strong></td>
<td>¼ cup</td>
</tr>
</tbody>
</table>

- Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. 57 (Level III)
### APPENDIX 3: Glycaemic Index of Foods

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Low GI (&lt;55)</th>
<th>Intermediate GI (56-70)</th>
<th>High GI (&gt;70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>Barley</td>
<td>Basmati Rice</td>
<td>Glutinous rice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brown rice</td>
<td>Jasmine rice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parboiled rice</td>
<td>Instant porridge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Red rice</td>
<td>White rice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sago</td>
</tr>
<tr>
<td>Bread and cereals</td>
<td>All bran breakfast cereals</td>
<td>Capati</td>
<td>Cornflakes</td>
</tr>
<tr>
<td>products</td>
<td>Muesli</td>
<td>Idli</td>
<td>Rice crackers</td>
</tr>
<tr>
<td></td>
<td>Wholegrain bread varieties</td>
<td>Oatmeal</td>
<td>Roti Canai</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pita bread, wholemeal</td>
<td>White flour bread</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wholemeal barley flour bread</td>
<td>Wholemeal (whole wheat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wheat flour bread</td>
</tr>
<tr>
<td>Noodle and Pasta</td>
<td>Lasagne pasta sheets, Spaghetti, white, boiled Spaghetti, wholemeal, boiled</td>
<td>Spaghetti, white, durum wheat semolina</td>
<td>Fried macaroni</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Udon noodles, plain Wheat noodles</td>
<td>Fried meeheoon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fried rice noodles</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rice noodle (kuih teow)</td>
</tr>
<tr>
<td>Milk</td>
<td>Full fat milk</td>
<td>Ice cream</td>
<td>Teh Tarik</td>
</tr>
<tr>
<td></td>
<td>Low fat milk</td>
<td>Sweetened condensed milk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skim milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soy milk (without added sugar)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yogurt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits</td>
<td>Apple</td>
<td>Banana</td>
<td>Lychee</td>
</tr>
<tr>
<td></td>
<td>Mango</td>
<td>Dates</td>
<td>Watermelon</td>
</tr>
<tr>
<td></td>
<td>Oranges</td>
<td>Papaya</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plum</td>
<td>Pineapples</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raisin</td>
<td></td>
</tr>
<tr>
<td>Legumes</td>
<td>Baked beans</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chickpeas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lentils</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mung bean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubers</td>
<td>Cassava, boiled</td>
<td>Pumpkins, boiled</td>
<td>Potato, boiled</td>
</tr>
<tr>
<td></td>
<td>Sweet potato, boiled</td>
<td>Sweet corn, boiled</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX 4: Assessment Prior to Intense Exercise

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Cardiovascular disease** | • Cardiovascular assessment should include a full history for cardiovascular symptoms. Where there is concern, referral to a cardiologist for further assessment is recommended.  
• There is no evidence of benefit for screening of asymptomatic patients, and adverse events are rare. In these patients, the most sensible approach is often to start with short periods of low-intensity exercise, and to increase both the intensity and the duration of exercise slowly.  
• Cardiovascular assessment is recommended for patients with autonomic neuropathy and/or proteinuria (microalbuminuria/macroalbuminuria) |
| **Peripheral neuropathy**  | • For patients with peripheral neuropathy, it is vital to ensure that appropriate footwear is worn and feet are examined regularly.  
• Weight-bearing exercise should be avoided in those with active foot disease and severe neuropathy, but moderate intensity walking may not increase the risk of ulceration and improves outcomes in milder neuropathy. |
| **Retinopathy**            | • It may be sensible to avoid vigorous exercise in the context of proliferative (or severe non-proliferative) retinopathy because of the risk of vitreous haemorrhage or retinal detachment. |
| **Nephropathy**            | • There is no evidence for the need for any specific exercise restriction in patients with diabetic renal disease.  
• Importantly, cardiovascular disease is increased in individuals with microalbuminuria or proteinuria, so cardiovascular assessment is recommended prior to exercise. |
| **Blood glucose**          | • If pre-exercise blood glucose is low normal (<5.6 mmol/L), advisable to take extra carbohydrate before exercise. This may not be necessary for short duration exercise or for those who are not taking insulin or insulin secretagogues. |

*Adapted from the American Diabetes Association Standards for Medical Care in Diabetes – 2015.* 

*Level III*
### APPENDIX 5: Grading of Physical Activities

<table>
<thead>
<tr>
<th>Mild Activities</th>
<th>Moderate Activities</th>
<th>Strenuous Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brisk walking on flat surfaces</td>
<td>Faster walking</td>
<td>Jogging</td>
</tr>
<tr>
<td>Cycling on level surface</td>
<td>Walking down stairs</td>
<td>Climbing stairs</td>
</tr>
<tr>
<td>Gardening, weeding</td>
<td>Cycling</td>
<td>Football</td>
</tr>
<tr>
<td>House painting</td>
<td>Doing heavy laundry</td>
<td>Squash</td>
</tr>
<tr>
<td>Mopping the floor</td>
<td>Ballroom dancing (slow)</td>
<td>Swimming</td>
</tr>
<tr>
<td>Cleaning windows</td>
<td>Badminton (non-competitive)</td>
<td>Playing single tennis</td>
</tr>
<tr>
<td>Golf – walking &amp; pulling</td>
<td>Aerobics (low impact)</td>
<td>Jumping rope</td>
</tr>
<tr>
<td>Bowling</td>
<td>Doing water Aerobics</td>
<td>Basketball</td>
</tr>
<tr>
<td></td>
<td>Playing doubles tennis</td>
<td>Cycling up hills</td>
</tr>
</tbody>
</table>

**Definition:**
- **Mild activities**: 35 to 50% of a person’s maximum heart rate.
- **Moderate activities**: 50 to 70% of a person’s maximum heart rate.
- **Strenuous activities**: >70% of a person’s maximum heart rate.

### Muscle Strengthening Exercise or Resistance Exercise

Activities to increase muscle strength and endurance minimum of 3 times per week:
- Should be progressive
- Involving major muscle groups
- Repetitive
- e.g. Lifting weights - dumbells or barbells

*Adapted from American College of Sports Medicine Position Stand. Progression Models in Resistance Training for Healthy Adults, 2009.*
### APPENDIX 6: Dosage of Anti-diabetic Agents in Renal Failure

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Usual Dose</th>
<th>Dose Adjustment in Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild (CKD 2) (GFR 60-89 ml/min)</td>
<td>Moderate (CKD 3) (GFR 30-59 ml/min)</td>
</tr>
<tr>
<td><strong>Biguanide§</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>500–1000 mg BD</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Sulphonylureas^</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>5 mg OD–10 mg BD</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80 mg OD–160 mg BD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Gliclazide MR</td>
<td>30–120 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1–4 mg OD</td>
<td>Initiate with 1 mg od</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5–15 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Meglitinides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5–4 mg TDS</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60–120 mg TDS</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Alpha-glucosidase Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose</td>
<td>25–100 mg TDS</td>
<td>50 - 100%</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4–8 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15–45 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg OD–BD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5–5 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>2.5–5 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>25 mg OD</td>
<td>25 mg od</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; GFR = glomerular filtration rate; OD = once daily; bd = twice daily; TDS = three time daily

^ Sulfonylureas should be used cautiously because of the increase risk of hypoglycaemia. First generation sulfonylureas (e.g. glibenclamide): generally should be avoided due to increased half-life and risk of hypoglycaemia in patients with CKD. Gliclazide and glimepiride are the preferred agents among the second generation sulfonylureas as they do not have active metabolites and have lower risk of hypoglycaemia in CKD patients.

§ Metformin is eliminated via kidney and may accumulate in body as kidney function deteriorates, increase risk of lactic acidosis.

* Modified from the Malaysian Clinical Practice Guidelines on Diabetic Nephropathy, 2004 and Clinical Practice Guidelines on Management of Chronic Kidney Disease in Adults. 280, 293 (Level III)
### APPENDIX 6: Dosage of Anti-diabetic Agents in Renal Failure (cont.)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Usual Dose</th>
<th>Dose Adjustment in Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild (CKD 2) (GFR 60-89 ml/min)</td>
<td>Moderate (CKD 3) (GFR 30-59 ml/min)</td>
</tr>
<tr>
<td><strong>GLP-1 Receptor Agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>5 mcg BD x 1 month, then 10 mcg BD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>2 mg weekly</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.6 mg OD x 1 week, then 1.2–1.8 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>10 mcg OD x 2 weeks, then 20 mcg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.75–1.5 mg weekly</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>SGLT2 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>5–10 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>100–300 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10–25 mg OD</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses should be adjusted based on frequent monitoring to balance goals of glycaemic control with avoiding hypoglycaemia. Long-acting tends to accumulate longer than short-acting insulin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; GFR = glomerular filtration rate; OD = once daily; bd = twice daily; TDS = three time daily

- Modified from the Malaysian Clinical Practice Guidelines on Diabetic Nephropathy, 2004 and Clinical Practice Guidelines on Management of Chronic Kidney Disease in Adults, 280, 293 (Level III)
APPENDIX 7: The 5-Item Version of the International Index of Erectile Function

1. How do you rate your confidence that you could get and keep an erection?

<table>
<thead>
<tr>
<th></th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

<table>
<thead>
<tr>
<th></th>
<th>No sexual activity</th>
<th>Never or almost never</th>
<th>A few times (much less than half the time)</th>
<th>Sometimes (about half the time)</th>
<th>Most times (much more than half the time)</th>
<th>Almost always or always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

<table>
<thead>
<tr>
<th></th>
<th>Did not attempt intercourse</th>
<th>Never or almost never</th>
<th>A few times (much less than half the time)</th>
<th>Sometimes (about half the time)</th>
<th>Most times (much more than half the time)</th>
<th>Almost always or always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erection Maintenance</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

<table>
<thead>
<tr>
<th></th>
<th>Did not attempt intercourse</th>
<th>Extremely difficult</th>
<th>Very difficult</th>
<th>Difficult</th>
<th>Slightly difficult</th>
<th>Not difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. When you attempted intercourse, how often was it satisfactory for you?

<table>
<thead>
<tr>
<th></th>
<th>Did not attempt intercourse</th>
<th>Never or almost never</th>
<th>A few times (much less than half the time)</th>
<th>Sometimes (about half the time)</th>
<th>Most times (much more than half the time)</th>
<th>Almost always or always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturation</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1. All questions are pertaining to the last 4 weeks
2. Total up all scores (maximum score = 25)
3. Classification of the Severity of ED:

<table>
<thead>
<tr>
<th>Total score</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Severe</td>
</tr>
<tr>
<td>8-11</td>
<td>Moderate</td>
</tr>
<tr>
<td>12-16</td>
<td>Mild / Moderate</td>
</tr>
<tr>
<td>17-21</td>
<td>Mild</td>
</tr>
<tr>
<td>22-25</td>
<td>No abnormality</td>
</tr>
</tbody>
</table>
Indeks Fungsi Seks Antarabangsa (IIEF-5) 349 (Level III)

Soalan-soalan ini bertanya tentang kesan ke atas kehidupan seks (kemampuan seks) anda akibat masalah ketegangan zakar (kemaluan atau 'batang' keras) di sepanjang 4 minggu yang lalu. Sila jawab soalan-soalan berikut dengan sejujur dan sejelas mungkin. Bagi menjawab soalan-soalan itu, definisi berikut adalah berkaitan:

- **Kegiatan seks** meliputi persetubuhan, belaian (rabaan, usapan), cumbuan dan perlancapan.
- **Persetubuhan** ditakrif sebagai kemasukan zakar (kemaluan) ke dalam faraj (pintu rahim) pasangan (zakar anda memasuki alat kelamin pasangan anda).
- **Rangsangan seks (naik nafsu seks)** meliputi keadaan seperti mencumbui pasangan, melihat gambaran erotik atau lucah, yang menaikkan rasa nafsu seks, dll.
- **Terpuncut** pemancutan air mani daripada zakar (atau perasaan seolah-olah berlaku pemancutan)

<table>
<thead>
<tr>
<th>1. Bagaimanakah anda menentukan kadar keyakinan yang kemaluan anda berfungsi dan dapat mengekalkan ketegangannya?</th>
<th>Sangat rendah</th>
<th>Rendah</th>
<th>Sederhana</th>
<th>Tinggi</th>
<th>Sangat Tinggi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiada Rangsangan seks</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Apabila anda mengalami ketegangan zakar (kemaluan atau 'batang' keras) menerusi rangsangan seks, berapa kerap kerap ketegangan itu cukup keras untuk persetubuhan?</th>
<th>Langsung tidak pernah/hampir tidak pernah</th>
<th>Beberapa kali (kurang daripada 50%)</th>
<th>Kadang-kadang (kira-kira 50%)</th>
<th>Sering kali (lebih dari 50%)</th>
<th>Setiap kali/Hampir setiap kali</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidak mencuba persetubuhan</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Sewaktu bersetubuh, berapa kerap anda dapat mengekalkan ketegangan kemaluan sehingga selesai persetubuhan?</th>
<th>Langsung tidak pernah/hampir tidak pernah</th>
<th>Beberapa kali (kurang daripada 50%)</th>
<th>Kadang-kadang (kira-kira 50%)</th>
<th>Sering kali (lebih dari 50%)</th>
<th>Setiap kali/Hampir setiap kali</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidak mencuba persetubuhan</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Sewaktu bersetubuh, berapa sukarkah untuk mengekalkan ketegangan kemaluan sehingga selesai persetubuhan?</th>
<th>Tersangat sukar</th>
<th>Sangat sukar</th>
<th>Sukar</th>
<th>Sukar sedikit</th>
<th>Tidak sukar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidak mencuba persetubuhan</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Apabila anda cuba melakukan persetubuhan, berapa kerap anda berasa puas hati?</th>
<th>Langsung tidak pernah/hampir tidak pernah</th>
<th>Beberapa kali (kurang daripada 50%)</th>
<th>Kadang-kadang (kira-kira 50%)</th>
<th>Sering kali (lebih dari 50%)</th>
<th>Setiap kali/Hampir setiap kali</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidak mencuba persetubuhan</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

1. Semua soalan, bermula dengan "Di sepanjang 4 minggu yang lalu"

2. Jumlahkan skor pada setiap item 1-5 (Jumlah skor yang mungkin = 25)

3. **Klasifikasi Keterukan ED:**

<table>
<thead>
<tr>
<th>Jumlah skor</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Sangat teruk</td>
</tr>
<tr>
<td>8-11</td>
<td>Sederhana</td>
</tr>
<tr>
<td>12-16</td>
<td>Ringan hingga sederhana</td>
</tr>
<tr>
<td>17-21</td>
<td>Ringan</td>
</tr>
<tr>
<td>22-25</td>
<td>Tidak ada masalah ED</td>
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</table>

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## APPENDIX 8 Categories of Risk in Diabetic Patients Who Fast During Ramadan

### Very high risk

- History of severe diabetes complications within 3 months prior to fasting:
  - Severe hypoglycaemia
  - Diabetic ketoacidosis
  - Hyperglycaemic hyperosmolar state
  - Recurrent hypoglycaemia
- Hypoglycaemia unawareness
- Type 1 diabetes
- Acute severe illness
- Sustained poor glycaemic control (A1c >9%)  
- Performing intense physical labour
- Pregnancy
- Advanced renal failure / chronic haemodialysis

### High risk

- Moderate hyperglycaemia (A1c 7.5–9.0%)
- Moderate renal failure
- Advanced macrovascular complications
- Living alone and treated with insulin or sulphonylureas
- Patients with comorbid conditions that present additional risk factors
- Old age with ill health
- Treatment with drugs that may affect mentation

### Moderate risk

- Well-controlled diabetes treated with short-acting insulin secretagogues

### Low risk

- Well-controlled diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, incretin-based therapies and/or SGLT2 inhibitors in otherwise healthy patients

- Adapted from “Recommendations for Management of Diabetes During Ramadan: Update 2010”. Diabetes Care, 2010. 434 (Level III)

### Note:

- This classification is based largely on expert opinion and not on scientific data derived from clinical studies.
- Those who fall in the “very high” and “high risk” group are advised to abstain from fasting.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>Glycated Haemoglobin</td>
</tr>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting Enzyme Inhibitor</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin-Creatinine ratio</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>ADI</td>
<td>Acceptable daily intake</td>
</tr>
<tr>
<td>AGI</td>
<td>a-glucosidase inhibitor</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin Receptor Blocker</td>
</tr>
<tr>
<td>BD</td>
<td>Twice daily (Bis Die)</td>
</tr>
<tr>
<td>BG</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>BUSE</td>
<td>Blood Urea And Serum Electrolytes</td>
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<tr>
<td>CAN</td>
<td>Cardiac autonomic neuropathy</td>
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<tr>
<td>CCB</td>
<td>Calcium Channel Blocker</td>
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<tr>
<td>CCF</td>
<td>Congestive Cardiac Failure</td>
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<tr>
<td>CCSI</td>
<td>Continuous subcutaneous insulin infusion</td>
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<tr>
<td>CCU</td>
<td>Coronary Care Unit</td>
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<tr>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CHO</td>
<td>Carbohydrate</td>
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<td>CKD</td>
<td>Chronic Renal Disease</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>DAN</td>
<td>Diabetic autonomic neuropathy</td>
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<tr>
<td>DCCT</td>
<td>Diabetes Control and Complications Trials</td>
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<tr>
<td>DHEA</td>
<td>Dehydroepiandrosterone</td>
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<td>DKA</td>
<td>Diabetes Ketoacidosis</td>
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<td>DM</td>
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<td>DN</td>
<td>Diabetic Nephropathy</td>
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<tr>
<td>DPN</td>
<td>Diabetic peripheral neuropathy</td>
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<tr>
<td>DPP-4i</td>
<td>Dipeptidyl peptidase-4 inhibitors</td>
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<tr>
<td>DR</td>
<td>Diabetic retinopathy</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ED</td>
<td>Erectile Dysfunction</td>
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<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
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<tr>
<td>ETDRS</td>
<td>Early Treatment of Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>FPG</td>
<td>Fasting Plasma Glucose</td>
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<tr>
<td>FRS</td>
<td>Framingham Risk Score</td>
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<td>FSD</td>
<td>Female sexual disorder</td>
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<tr>
<td>FSFI</td>
<td>Female Sexual Function Index</td>
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<tr>
<td>GDM</td>
<td>Gestational Diabetes Mellitus</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GI</td>
<td>Glycaemic Index</td>
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<tr>
<td>GIP</td>
<td>Glucose-dependent Insulinotropic Polypeptide</td>
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<tr>
<td>GLP-1 RA</td>
<td>Glucagon-like Peptide 1 Receptor Agonist</td>
</tr>
<tr>
<td>HDL</td>
<td>High Density Lipoprotein</td>
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<tr>
<td>HDU</td>
<td>High Dependency Unit</td>
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<tr>
<td>HHS</td>
<td>Hyperglycaemic Hyperosmolar Syndrome</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
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<tr>
<td>IFG</td>
<td>Impaired Fasting Glucose</td>
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<tr>
<td>IGT</td>
<td>Impaired Glucose Tolerance</td>
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<tr>
<td>IIEF</td>
<td>International Index of Erectile Dysfunction</td>
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<tr>
<td>JPAD</td>
<td>Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes</td>
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<tr>
<td>LAGB</td>
<td>Laproscopic Adjustable Gastric Banding</td>
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<tr>
<td>LBW</td>
<td>Low Birth Weight</td>
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<tr>
<td>LDL</td>
<td>Low Density Lipoprotein</td>
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<tr>
<td>LGA</td>
<td>Large for Gestational Age</td>
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<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
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<tr>
<td>LSCS</td>
<td>Lower Segment Caesarean Section</td>
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<tr>
<td>MADRAC</td>
<td>Malaysian Adverse Drug Reaction Advisory Committee</td>
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<tr>
<td>MDI</td>
<td>Multiple Daily Injection</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<td>MNT</td>
<td>Medical Nutrition Therapy</td>
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<td>MRP</td>
<td>Meal replacement</td>
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<td>NAFLD</td>
<td>Non-alcoholic Fatty Liver Disease</td>
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<td>NCEP</td>
<td>National Cholesterol Education Program</td>
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<td>NICE</td>
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<tr>
<td>NPDR</td>
<td>Non-proliferative Diabetic Retinopathy</td>
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<tr>
<td>NPH</td>
<td>Neutral Protamine Hagedorn</td>
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<tr>
<td>NSAIDs</td>
<td>Non-steroidal Anti-inflammatory Drugs</td>
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<tr>
<td>OAD</td>
<td>Oral Anti-diabetic</td>
</tr>
<tr>
<td>OD</td>
<td>Once Daily (Omni Die)</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>OM</td>
<td>On Morning (Omni Mane)</td>
</tr>
<tr>
<td>ON</td>
<td>On Night (Omni Nocte)</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>OSAS</td>
<td>Obstructive Sleep Apnoea Syndrome</td>
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<tr>
<td>PCOS</td>
<td>Polycystic Ovarian Syndrome</td>
</tr>
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<td>PDE-5</td>
<td>Phospodiesterase-5</td>
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<tr>
<td>PN</td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>POPADAD</td>
<td>Prevention of Progression of Arterial Disease and Diabetes</td>
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<tr>
<td>PPAR-γ</td>
<td>Peroxisome Proliferator-Activated Receptor-Gamma</td>
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<tr>
<td>PPG</td>
<td>Post-prandial Plasma Glucose</td>
</tr>
<tr>
<td>RPG</td>
<td>Random Plasma Glucose</td>
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<tr>
<td>SBMG</td>
<td>Self Blood Monitoring Glucose</td>
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<tr>
<td>SC</td>
<td>Subcutaneous</td>
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<tr>
<td>SCORE</td>
<td>Systematic Coronary Risk Evaluation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for Gestational Age</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of Inappropriate Antidiuretic Hormone</td>
</tr>
<tr>
<td>SSB</td>
<td>Sugar Sweetened Beverage</td>
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<tr>
<td>SSI</td>
<td>Sliding Scale Insulin</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Receptor Inhibitor</td>
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<tr>
<td>SU</td>
<td>Sulphonylurea</td>
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<tr>
<td>T1DM</td>
<td>Type 1 Diabetes Mellitus</td>
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<tr>
<td>T2DM</td>
<td>Type 2 Diabetes Mellitus</td>
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<tr>
<td>TDD</td>
<td>Total daily dose</td>
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<tr>
<td>TDS</td>
<td>Three Times Daily (Ter Die Sumendus)</td>
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<tr>
<td>TG</td>
<td>Triglycerides</td>
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<tr>
<td>TZD</td>
<td>Thiazolidinedione</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>WC</td>
<td>Waist Circumference</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
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All the members of the development group have completed their conflict of interest disclosure forms. None of them holds any shares or acts as full-time consultants in any of the pharmaceutical companies. Details of these disclosures are available upon request by writing to the CPG secretariat.

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The definition of types of evidence and the grading of recommendation used in this guideline originate from the U.S./Canadian Preventive Services Task Force and are set out in the following tables:

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one properly randomized controlled trial</td>
</tr>
<tr>
<td>II – 1</td>
<td>Evidence obtained from well-designed controlled trials without randomization</td>
</tr>
<tr>
<td>II – 2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group</td>
</tr>
<tr>
<td>II – 3</td>
<td>Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees</td>
</tr>
</tbody>
</table>

Source: U.S./Canadian Preventive Services Task Force

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population</td>
</tr>
<tr>
<td>B</td>
<td>Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT</td>
</tr>
<tr>
<td>C</td>
<td>Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

Source: Modified From Scottish Intercollegiate Guidelines Network (SIGN)