DECEMBER 2020

MOH/P/PAK/447.20(GU)-e

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

(6th Edition)

Malaysia Endocrine & Metabolic Society

Ministry of Health Malaysia

Academy of Medicine Malaysia

Diabetes Malaysia

Family Medicine Specialists Association of Malaysia

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MANAGEMENT OF TYPE 2 DIABETES MELLITUS

(6TH EDITION)

This is the revised and updated Clinical Practice Guidelines (CPG) on Management of Type 2 Diabetes Mellitus (T2DM). The recommendations in this 6th edition CPG supersedes the 5th edition Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus 2015.

STATEMENT OF INTENT

This guideline is meant for the clinical management of T2DM, 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 healthcare provider is responsible for the individualised management of his/her patient based on patient presentation and management options available locally.

REVIEW OF THE GUIDELINES

These guidelines issued in December 2020, will be reviewed in 5 years (2025) 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

FOREWORD

by Tan Sri Dato' Seri Dr Noor Hisham Abdullah, Director General of Health, Malaysia

Management of any chronic disease requires a concerted effort with the participation of all stake holders starting with the patients themselves and, clinical healthcare professionals as well as public health policymakers. This is even more important in the management of Type 2 diabetes mellitus (T2DM). An optimum result can only be achieved with a holistic approach and active patient participation with the support of appropriate diabetes education and lifestyle modification. In addition to its negative impact on the quality of life and health care costs, diabetes also increases the economic burden of individuals, families and communities and, affects national productivity.

I note that there has been a recent explosion of advances made in the management of diabetic complications. The use of new technology and findings from landmark trials have changed clinical pathways and recommendations in the way T2DM is managed. This has been reflected in the latest Clinical Practice Guidelines (CPG) for the Management of T2DM (6th Edition). These guidelines also focus on preventing and reducing diabetes-related complications, thereby improving clinical outcomes. This CPG will form a valuable resource for healthcare professionals from primary to tertiary care levels, to deliver the best possible care for their patients, from disease prevention to treatment of complications.

In this networked age, we should no longer be working in silos and I would like to reaffirm the importance and recognition of a multidisciplinary approach in managing T2DM. I have been a champion for embracing technology and innovation – and note that there is emphasis on the potential to use mobile apps and other forms of technological advances / telemedicine to improve diabetes self-management. The importance of this is even greater now in the context of the new norm forced on everyone by the Covid-19 pandemic.

The breadth and depth of material covered reflects the commitment and the dedication of the CPG committee, despite the difficulties encountered during the Covid-19 pandemic. I would like to congratulate the chairs and the members for their hard work and it is my sincere wish that this document will further elevate the standard of diabetes care and reduce the burden of T2DM in our country.

Tan Sri Dato' Seri Dr Noor Hisham Abdullah

FOREWORD

by Chairpersons of T2DM Clinical Practice Guidelines, 6th edition taskforce

These are exciting times for the treatment of Type 2 diabetes mellitus (T2DM) and a time for concern. The past 5 years have seen amazing breakthroughs that give hope for people with T2DM. Several Cardiovascular Outcome trials (CVOTs) from 2 new classes of glucose-lowering agents have shown cardiovascular (CV) protection, beyond glucose.

On the other hand, prevalence of diabetes in Malaysia continues to rise unabated. The 2019 National Health and Morbidity Survey (NHMS) shows a prevalence of 18.3% (for adults >18 years of age), a 4% increase from 2015; 48.6% were undiagnosed. In addition, ~5.0% of our young Malaysians between 18-29 years are also diabetic. It is worrying to see this trend. The frequent co-existence with other well-known comorbidities, e.g. hypertension, dyslipidaemia, overweight/obesity further complicates the situation.

The 5th edition of our Clinical Practice Guidelines (CPG) for the Management of T2DM 2015, was detailed and comprehensive. Our aspiration was to build on the previous CPG. Since then, there have been major advances; in therapeutics, nutrition, technology as well as, digital health.

The landmark CVOTs have consistently demonstrated positive beneficial CV outcomes in those with either established or at high risk for cardiovascular disease (CVD). Another exciting advance has been the discovery of a 2nd therapeutic class of agent, apart from the renin-angiotensin system blockers, to directly reduce progression of diabetic kidney disease (DKD). DKD remains the largest contributor of new patients requiring dialysis in Malaysia and, recent renal outcome trials definitively show positive outcomes for prevention of progression to end-stage renal failure and reduction of albuminuria. More exciting data may be forthcoming with ongoing dedicated trials investigating effects of these glucose-lowering agents, on heart failure and prevention of kidney disease not only in people with diabetes but also, in nondiabetic individuals.

These results have led to paradigm shifts, changing practices as we move forward. The objective of these guidelines is to reflect the uptake of this new data in clinical decision making and therefore, provide evidence-based recommendations to assist healthcare providers in identifying, diagnosing and managing our patients with T2DM. Some of the other notable updates, include additional sections on current hot topics; e.g. non-alcoholic fatty liver disease

(NAFLD) and periodontal disease. The landmark CVOTs have been consolidated and summarised in Appendix 8.

T2DM is not a stand-alone disease instead reaching across a spectrum of other non-communicable diseases. Hence, in this updated guideline, we expanded our taskforce to include colleagues from other specialities; including nephrology, neurology, gastroenterology-hepatology, cardiology, ophthalmology, psychiatry and dental surgery. The committee hopes that this combination of expertise has enhanced the recommendations in this CPG to further improve clinical decision making.

The development of these guidelines extended into an extraordinary situation caused by the COVID-19 pandemic. Through it, the hardworking committee members of the taskforce, including our reviewers, persevered with continuous and timely discussions to reach consensus where required through use of technology/remote communication, enabling its completion. To this, we extend our appreciation and gratitude, and commend their unwavering commitment to deliver the best evidence-based standard of care to our patients with T2DM.

Dr Chan Siew Pheng
Chairperson

Dato' Paduka Professor Dr Wan Mohamad Wan Bebakar
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Co-chair

TERMS OF REFERENCE

Guidelines development

The guidelines development task force consisted of endocrinologists, paediatric endocrinologists, family medicine specialists, public health physicians, general physicians and dietitians. Where relevant, experts from different specialties were also included to review and update certain sub-sections within these guidelines. These included a nephrologist, neurologist, gastroenterologist-hepatologist, cardiologist, ophthalmologist, psychiatrist, dental surgeon, pharmacist and diabetes educator.

The previous edition of the CPG on Management of T2DM 2015 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) and Journal full text via OVID search engine. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies.

Reference was also made to the lastest edition of other guidelines on the management of T2DM including guidelines developed by the American Diabetes Association (ADA) Standards of Medical Care in Diabetes, American Association of Clinical Endocrinologists', American College of Endocrinology, International Diabetes Federation (IDF) Global Guideline for Type 2 Diabetes, the European Association for the Study of Diabetes (EASD), National Institute For Health and Care Excellence (NICE); Malaysian CPG on Management of Obesity, Canadian Diabetes Association, The Royal Australian College of General Practitioners and Diabetes Australia, Malaysian Dietitians' Association, Trafford NHS Healthcare Trust and Joint British Diabetes Societies Inpatient Care Group.

These updated guidelines also include the latest cardiovascular outcome trials (CVOTs) and findings from systematic reviews and meta-analyses in literature, all whilst taking into consideration local practices.

Clinical questions were divided into major subgroups and members of the task force were assigned individual topics within these subgroups. 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 Canadian Task Force on the Periodic Health Examination, while the grading of recommendation in this guideline was standardised with the previous edition of the T2DM CPG (5th edition) i.e. following the American Heart Association system, for easy comparison. The rationale for the committee to do so is that the format for both are familiar to our healthcare professionals and facilitates the CPG's ease of use.

The draft guidelines as a whole were submitted for external review by experts in endocrinology (adult and paediatric) and family medicine, whilst relevant sub-sections by consult with a neurologist, nephrologist, gastroenterologist-hepatologist, cardiologist, ophthalmologist, diabetes educator, psychiatrist and dental surgeon. These guidelines were then 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 these guidelines is to provide evidence-based recommendations to assist healthcare providers in the identification, diagnosis and management of patients with T2DM.

Clinical questions

1. What are the most effective methods to diagnose diabetes and pre-diabetes individuals and, strategies to detect symptomatic and asymptomatic individuals, including adolescents?
2. What team-based structured diabetes educational interventions and initiatives have been proven to successfully improve patient self-management?
3. What nutrition interventions have been proven to effectively prevent, delay the development of T2DM or reverse diabetes in recently diagnosed T2DM individuals?
4. What are the recommended indications for self-blood glucose monitoring (SMBG) in T2DM and the role of mobile health in this form of monitoring strategy?
5. What are the thresholds for BP levels for initiation of anti-hypertensive medication in individuals with T2DM and what are the BP targets?

6. How are patients risk stratified for LDL-lowering therapy in T2DM?
7. Has metabolic surgery come-of-age in the management of obese patients with T2DM and what is its role?
8. How prevalent is NAFLD in individuals with T2DM and what is its clinical significance?
9. What is the recommended practical approach to treat diabetic emergencies?
10. What does the evidence say about the possibility of delaying progression of DKD to ESKD?
11. How should the CV benefits documented in the recent landmark CVOTs in T2DM patients with established CVD or high risk of CVD influence clinical management?
12. Is diabetes distress/depression a common problem and how does it influence diabetes management?
13. How does periodontal disease affect management of T2DM and how can it best be managed?
14. What are the effective and safe management strategies of individuals with T2DM in the following situations?
    a. In acute illness/pre- and post-operation
    b. In the elderly with a special focus on cognitive assessment/dementia and co-morbidities
    c. During Ramadan
15. How should complementary and alternative medicine be addressed in the holistic management of T2DM?

Updated and new contents:

Major changes in these guidelines are:

1. Inclusion of Periodontal disease, Peripheral arterial disease and Non-alcoholic fatty liver disease.
2. Inclusion of Summary of Updates at the beginning of each chapter which, highlights the important new advances and issues requiring emphasis.
3. Replacement of the term chronic kidney disease (CKD) to diabetic kidney disease (DKD).
4. Replacement of the term oral anti-glycaemic drugs (OAD) to oral glucose lowering drugs (OGLDs) and glucose lowering drugs (GLD).

5. Diabetes in pregnancy is not included as it has its dedicated CPG on Management of Diabetes in Pregnancy launched in 2018. (Available at: *http://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/1a.pdf*).

All other changes and updates within the contents of these guidelines can be found in the Summary of Updates.

Target population

This guideline is applicable to all adolescents and adults at risk of developing and with T2DM.

Target audience

These guidelines are meant for all healthcare professionals involved in treating patients with T2DM which include: 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.

This 6th edition of the Clinical Practice Guidelines for the Management of T2DM was solely funded by the Malaysian Endocrine and Metabolic Society. All authors in the editorial committee have no conflicts of interests to declare.

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SECTION 1

INTRODUCTION: TYPE 2 DIABETES MELLITUS, THE DISEASE

1.1 Background

- Plasma glucose abnormalities may span a progressive continuum ranging from prediabetes, consisting of impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT), to overt diabetes mellitus.
- Prediabetes usually does not cause symptoms and is characterised by elevated plasma glucose levels that fall below the threshold to diagnose diabetes. Prediabetes is an important risk factor for future diabetes and cardiovascular disease (CVD). It is a potentially reversible condition with lifestyle modification.
- T2DM is the most common form of diabetes mellitus, accounting for >90% of all cases of adult-onset diabetes mellitus in Malaysia. Both prediabetes and diabetes commonly coexist with other non-communicable diseases namely hypertension, dyslipidaemia and obesity.
- With a high and increasing global, and local prevalence, T2DM represents a huge socio-economic burden due to increased morbidity from accelerated vascular complications and premature death.
- T2DM is characterised by progressive decline in beta-cell function associated with insulin resistance in muscle and adipose tissue.
  - The insulin resistant state results in increased hepatic glucose output and reduced utilisation of glucose by various organs contributing to fasting hyperglycaemia and between meal hyperglycaemia.
  - Impaired intestinal incretin secretion causes compromised meal-related insulin secretion and glucagon suppression contributing to postprandial hyperglycaemia.
  - Excessive renal tubular reabsorption of glucose further contributes to hyperglycaemia.
- T2DM is an important risk factor for CVD and microvascular complications such as nephropathy, retinopathy and neuropathy. Other non-vascular complications include infective complications.

- Non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnoea and an increased risk of certain malignancies are common co-morbidities that are associated with T2DM.
- The main aim of management is directed at reducing acute and chronic diabetes-related complications by targeting control of plasma glucose, BP, lipids and body weight concurrently.
- Recently, there is evidence that reversal or remission of T2DM may be possible in some individuals with short duration of disease, following reversal of insulin resistance through significant and sustained weight loss by either caloric restriction or bariatric surgery.

1.2 Prevalence and state of T2DM in Malaysia

- The National Health and Morbidity Survey (NHMS) 2019[1] (Level II-3) reported a prevalence of 23.6% for those with abnormal fasting plasma glucose (FPG) in non-diabetic range (FPG 5.6 mmol/L-6.9 mmol/L) at the time of the survey. This estimates approximately 5 million (5,019,359) adult individuals in Malaysia with probable prediabetes in 2019 and future risk of diabetes.
- Prevalence of a known or established diagnosis of diabetes during the 2019 NHMS was 9.4%, whilst in 2015 it was 8.3%.[2] (level II-3) Hence in 2019, there were almost 2 million (1,999,450) adult individuals with known diabetes in Malaysia.
- Prevalence of unknown/undiagnosed diabetes (elevated fasting plasma glucose of ≥7.0 mmol/L during survey) for adults age ≥18 years; in NHMS 2015 and 2019 were 5.1% and 8.9% respectively.[1,2] (Level II-3)
  - In 2019, there was an estimated 1,892,515 adult individuals with unknown/undiagnosed diabetes in Malaysia.
  - 42% of those with unknown diabetes are between the age of 18-39 years, and 40% are between the age 40-59 years.
- Overall diabetes prevalence in adults ≥18 years in NHMS 2015 and 2019 was 13.4% and 18.3% respectively.[1,2] (Level II-3) Prevalence for overall diabetes for adults age 30 years and above was 24.1% in NHMS 2019.
- Prevalence of overall diabetes among the major ethnic groups in the NHMS 2019 showed a similar trend as previous data which was 31.4%, 22.6% and 15.1% among the Indians, Malays and Chinese, respectively.[1] (Level II-3)

Table 1-1: Prevalence of overall diabetes by ethnicity for adults ≥18 years

	Overall diabetes	Diagnosed/ Known diabetes	Raised plasma glucose ≥7mmol/L / Unknown diabetes
Malay	22.6%	11.1%	10.6%
Chinese	15.1%	8.5%	6.6%
Indians	31.4%	18.5%	12.9%
Bumiputera Sabah	11.1%	4.7%	6.4%
Bumiputera Sarawak	12.2%	7.9%	4.3%
Others	8.7%	2.0%	6.7%
Others	8.7%	2.0%	6.7%

Sourced from NHMS 2019.[1 (Level II-3)]

- Prevalence of overall diabetes is increasing in the young with 4.3% and 5.4% of those between ages 18-19 years and 20-24 years, respectively.[1 (Level II-3)]

Table 1-2: Prevalence of overall diabetes by age group

Age Group	Overall diabetes
18-19	4.3%
20-24	5.4%
25-29	6.8%
30-34	11.2%
35-39	12.1%
40-44	17.2%
45-49	24.7%
50-54	30.4%
55-59	31.2%
60-64	42.4%
65-69	43.4%
70-74	40.6%
≥75	38.4%

Sourced from NHMS 2019.[1 (Level II-3)]

- According to the latest NHMS 2019,[1] >70% of diagnosed T2DM patients seek care in Ministry of Health (MoH) primary health clinics.
  - As part of the MoH's quality assurance program for diabetes care at the primary care level, a Diabetes Clinical Audit is conducted annually on randomly selected T2DM patients, with data collected through the National Diabetes Registry (NDR).
  - Currently there are 886,138 active T2DM patients on follow-up in MoH health clinics registered in the NDR.[3 (Level II-3)]
- From the 2019 Diabetes Clinical Audit, involving 181,627 T2DM patients, the mean HbA_{1c} was 7.9%; with 32.4% achieving HbA_{1c} <6.5%. This was an improvement from 2013, where the mean HbA_{1c} was 8.1% and only 20.4% achieved HbA_{1c} <6.5%.[3 (Level II-3)]
- Among individuals with known diabetes in the NHMS 2019, it was reported that 25.7% were treated with insulin, 85.6% with OGLDs and 88.0% had received advice on diet.
- Insulin use was higher overall in MoH clinics and hospitals compared to private clinics and hospitals.

Table 1-3: Percentage of patients on insulin by institution

	Percentage on insulin
Overall	25.7%
MoH clinic	26.0%
Private clinic	11.5%
MoH hospital	38.3%
Private hospital	30.5%

Sourced from NMHS 2019.[1 (Level II-3)]

Comorbidities

- From the same 2019 Diabetes Clinical Audit (NDR), the following were noted:[3 (Level II-3)]
  - prevalence of hypertension was 80.4% (hypertensive or on BP lowering therapy).
    - Mean systolic BP was 135.4 mmHg and diastolic BP was 76.9 mmHg.
    - BP <135/75 mmHg was achieved in 29.4% patients.
  - prevalence of dyslipidaemia was 74.3% (elevated total cholesterol [TC] or on lipid-lowering therapy).
    - Mean TC was 4.9 mmol/L (<4.5 mmol/L in 39.0%).
    - Mean low density lipoprotein-cholesterol (LDL-C) was 2.9 mmol/L (<2.6 mmol/L in 45.2%).

› 84.0% of individuals with T2DM are either overweight or obese (Body mass index [BMI] >23.0 kg/m^2).
  - Mean BMI was 27.8 kg/m^2
  - Mean waist circumference in males was 95.2 cm (>90 cm in 69.6%) and in females was 92.1 cm (>80 cm in 87.8%).

Complications

- In the 2015-2016 annual report of patients admitted with acute coronary syndrome (National Cardiovascular Disease Database – NCVD-ACS registry), 44.7% of patients were diagnosed to have diabetes. This is the 2nd-most common CV risk factor; the most prevalent CV risk was hypertension at 63.3%.[4 (Level II-3)]

- In 2016, diabetic kidney disease (DKD) was the most common cause of end stage kidney disease (ESKD), accounting for 65% of new patients requiring dialysis in Malaysia.[5 (Level II-3)]

Management

Refer to Table 1-4 for a summary of treatment use in individuals with T2DM based on the 2019 Diabetes Clinical Audit (NDR).[3 (Level II-3)]

Table 1-4: Summary of treatments used for T2DM management (Diabetes Clinical Audit, NDR 2019)

Medication		
Glucose lowering therapy		
Diet alone		5.6%
Most commonly prescribed	Metformin Sulphonylureas	83% 44%
Number of medications	OGLD monotherapy ≥2 OGLDs	28.9% 35.1%
Insulin use	Overall In combination with OGLD*	30.3% 23.7%
Anti-hypertensive therapy		
Most commonly prescribed	Calcium channel blockers ACE-i	57.7% 51.8%
Other medications		
Lipid lowering agents **Anti-platelet agents**	Statins Aspirin	79.9% 19.2%

** Insulin in combination with OGLDs (overall population); the total % of patients on medications do not add up to 100% due to missing data. OGLDs: oral glucose lowering drugs; ACE-i: angiotensin converting enzyme inhibitor. Sourced from Diabetes Clinical Audit, NDR.[3 (Level II-3)]*

SECTION 2

SCREENING AND DIAGNOSIS

SUMMARY OF UPDATES

- Risk-based screening for pre-diabetes and/or T2DM in adults should be performed in individuals >30 years of age and repeated annually.
- In symptomatic individuals, 1 abnormal result (either plasma glucose/ HbA_{1c}) is diagnostic while in asymptomatic individuals, 2 abnormal test results from the same sample (e.g. plasma glucose + HbA_{1c}) or from 2 separate test samples are accepted for diagnosis.
- Recommendations for criteria-based screening of adolescents who are overweight and have additional risk factors for T2DM ***(NEW)***.

2.1 Objective and strategies

Objective

- To diagnose prediabetes and T2DM among the general population specifically the high-risk individuals, whilst ensuring prompt and appropriate intervention.

Strategies

- Screening the general population to identify high-risk individuals.
- Screening of specific high-risk populations e.g. those with history of gestational diabetes mellitus (GDM).

2.2 Who should be screened

- Symptomatic individuals
  - › Any individual who has symptoms suggestive of T2DM (fatigue, lethargy, polyuria, nocturia, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) should be investigated to confirm diagnosis of T2DM.[6] (Level III)

- Asymptomatic individuals
  - From our National Health and Morbidity Survey (NHMS) data,[1] (Level II-3) 48.6% of individuals with diabetes were undiagnosed at time of screening. Recognising that up to 50% of individuals with diabetes are asymptomatic makes the case for screening when specific risk factors are present.

Table 2-1: Criteria for testing for T2DM or prediabetes in asymptomatic adults

A. Women with history of GDM

B. Adults who are overweight or obese (Body mass index [BMI] ≥23 kg/m^2 or waist circumference ≥80 cm for women and ≥90 cm for men) with ANY of the following*:

- History of CVD
- 1° relatives with T2DM
- Hypertension (BP ≥140/90 mmHg or on therapy for hypertension)
- HDL-C <0.9 mmol/L or TG >2.8 mmol/L
- Women who have delivered a baby weighing ≥4 kg
- Those who were born from mothers with GDM
- Other endocrine conditions associated with insulin resistance e.g.
  - PCOS
  - Cushing's syndrome
  - Acromegaly
  - Phaeochromocytoma
  - Presence of acanthosis nigricans
- Physical inactivity and sedentary lifestyle
- Those receiving long-term treatment with any of the following:
  - corticosteroids
  - anti-retroviral therapy
  - atypical anti-psychotic drugs
  - thiazide diuretics
  - β-adrenergic blockers
  - 3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors [statins]

Note: In those without the above risk factors, testing should begin at the age of 30 years. If tests are normal, screening should be performed annually.[7] (Level III)

C. All individuals with prediabetes (HbA_{1c} ≥5.7%-6.2% [39 mmol/mol-44 mmol/mol], IGT, or IGF) should be tested yearly.

Adapted from the American Diabetes Association Standards of Care in Diabetes 2020.[6] (Level III)

Table 2-2: Criteria for testing for T2DM in adolescents

Screening should be performed in adolescents* who are overweight (85th percentile) or obese (95th percentile), and who have one or more additional risk factors such as:

- maternal history of diabetes or GDM during the child's gestation
- family history of T2DM in a 1° relative
- recurrent abscess and/or pruritus genitalia
- signs of insulin resistance or conditions associated with insulin resistance (dyslipidaemia, hypertension, polycystic ovary syndrome, acanthosis nigricans or small for gestational age birth weight)

If tests are normal, repeat screening at a minimum of 3-year intervals, or more frequently if BMI is increasing.

**After the onset of puberty or after 10 years of age, whichever occurs earlier.*
Adapted from the American Diabetes Association Standards of Care in Diabetes 2020.[6 (Level III)]

2.3 Screening test

Capillary plasma glucose

- In circumstances where facilities for venous plasma glucose measurements are not readily available, preliminary screening can be performed by measuring capillary plasma glucose using standard glucometers.
  - › This testing can be done irrespective of timing of prior meals.
  - › If the random capillary plasma glucose ≥7.8 mmol/L or fasting ≥5.6 mmol/L, a confirmatory test needs to be performed by one of the following methods
    - fasting plasma glucose (FPG)
    - oral glucose tolerance test (OGTT)
    - HbA_{1c}
- Screening should be done annually in those listed in Tables 2-1 and 2-2.

2.4 Diagnostic tests

- Fasting plasma glucose
  - › This should be performed following a minimum of an 8-hour overnight fast.
  - › Once blood is taken, the sample should not be left standing as the concentration of glucose decreases due to glycolysis, which degrades glucose at a rate of 5% to 7% per hour.[8 (Level II-2)]

- This glycolysis can be prevented by using sample tubes containing glycolysis inhibitors such as citrate buffer.
- Patient is considered to have prediabetes/IFG if the FPG is between 6.1-6.9 mmol/L and diabetes if the FPG is ≥7.0 mmol/L (Refer Table 2-3 and, Figures 2-1 and 2-2).

Table 2-3: Diagnostic value for T2DM based on venous plasma glucose

	Fasting	Random
Venous plasma glucose	≥7.0 mmol/L	≥11.1 mmol/L

In symptomatic individuals, one abnormal glucose value is diagnostic. In asymptomatic individuals, 2 abnormal test results (plasma glucose and HbA_{1c}) from the same sample or from 2 separate test samples are required for diagnosis.

- Oral glucose tolerance test (OGTT)
  - OGTT is done in the fasting state using 75 g of glucose.
  - Patient should rest throughout the test and only allowed to drink plain water.
  - A 2-hour plasma glucose of ≥11.1 mmol/L confirms the diagnosis of diabetes.
  - Patient is considered to have IGT of prediabetes if the 2-hour plasma glucose level is between 7.8-11.0 mmol/L (Refer Table 2-4 and, Figures 2-1 and 2-2).

Table 2-4: Diagnostic value for glucose tolerance and T2DM based on OGTT

OGTT plasma glucose values (mmol/L)		
Category	**0-hour**	**2-hour**
Normal	<6.1	<7.8
IFG	6.1-6.9	-
IGT	-	7.8-11.0
T2DM	≥7.0	≥11.1

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus. In adolescents, the glucose load in OGTT is based on body weight (1.75 g/kg body weight, maximum of 75 g).

- HbA_{1c}
  - HbA_{1c} reflects the average plasma glucose level over the preceding 3 months.[9 (Level I)]
  - Although OGTT used to be the "gold standard" for diagnosing T2DM, it is known to be poorly reproducible and is cumbersome to perform.[10 (Level II-2)]
  - Standardised HbA_{1c} assay has been shown to have the least variability (0.3%-0.4%) compared to fasting and 2-hour plasma glucose levels, 12% and 20% respectively.[11 (Level II-2)]

- Using HbA_{1c} to diagnose is convenient as it does not require the individual to fast or consume oral glucose, and it can be performed at any time of the day.[10-15 (Level II-2)]
- Based on the Metabolic Syndrome Study of Malaysia (MSSM) 2009, involving 4,400 adults, a HbA_{1c} level of 6.3% has a positive predictive value of 58% and negative predictive value of 84%.
  - HbA_{1c} at this level was found to give the maximal acceptable sum of specificity and sensitivity of 97% and 42.5%, respectively in diagnosing T2DM for all three major ethnic groups in this country.
- Diagnosing T2DM based on HbA_{1c} of 6.5% however leads to a lower unacceptable sensitivity of 36.7%.
  - These data are based on correlation between HbA_{1c} levels and 75-gram OGTT results where the receiver-operating characteristic (ROC) curve obtained was 0.85, consistent with other similar studies.
- Individuals with HbA_{1c} between 5.7% and 6.2% will be deemed as having prediabetes.
  - At HbA_{1c} level of 5.7%, the sensitivity and specificity of diagnosing prediabetes were 78% and 79% respectively.
  - If HbA_{1c} is used for the diagnosis of prediabetes, it is best that the test is followed by an OGTT to classify individuals into either IFG, IGT or combination of both.[16,17 (Level II-2)]
  - This has prognostic significance in terms of the risk of developing CVD and conversion to frank T2DM.

Table 2-5: Diagnostic value for prediabetes and T2DM based on HbA_{1c}

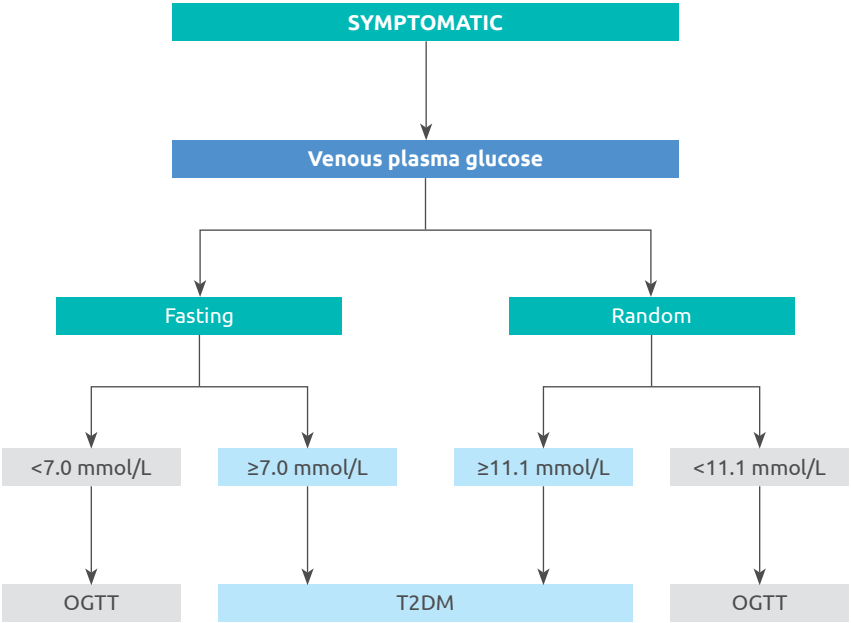
	Normal	Prediabetes	T2DM
HbA_{1c}	<5.7% (<39 mmol/mol)	5.7%-<6.3% (39-44 mmol/mol)	≥6.3% (≥45 mmol/mol)

A repeat HbA_{1c} should be done 4 weeks after the first positive test for asymptomatic patients (if an accompanying FPG or RPG is indeterminate). For symptomatic patients, a single positive test is sufficient. FPG: fasting plasma glucose; RPG: random plasma glucose

- There are situations where the HbA_{1c} value may not reflect the true level of glycaemia (glycation gap) due to various causes (Refer to Section 3.8.1).[18,19]
  - Depending on the method used for measuring HbA_{1c}, some may give inaccurate results when the patients have a haemoglobin variant.[20,21 (Level III)]
    - » In patients suspected of having haemoglobinopathies, other screening tests for e.g. another HbA_{1c} methodology should be used (such as the National Glycohemoglobin Standardization Program [NGSP] available online at *http://www.ngsp.org/interf.asp*).

- HbA_{1c} is not appropriate for the diagnosis of diabetes in:
  - adolescents (<18 years old) since the diagnostic cut-off point was derived in those >18 years,
  - patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics,
  - patients taking iron supplements (may falsely lower HbA_{1c} levels),
  - patients with acute pancreatic damage, including pancreatic surgery,
  - presence of genetic, haematologic and illness-related factors that influence HbA_{1c} and its measurement (e.g. haemoglobinopathies, rheumatoid arthritis, chronic liver disease, post-splenectomy),
  - patients with chronic kidney disease (CKD) stages 4 or 5 and those on erythropoietin injections; and
  - anaemia due to iron, vitamin B_{12} or erythropoietin deficiencies.
- HbA_{1c} reporting and the new SI units
  - Glycaemic control in patients with diabetes is assessed using HbA_{1c}.
    - The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) clearly demonstrated the correlation of an increasing HbA_{1c} with the increased risk of complications.[22-24 (Level I)]
    - Hence, for HbA_{1c} to be useful, it is important that the HbA_{1c} assays are standardised.
    - Several international and national standardisation programs have evolved over the years to enable the conformity of HbA_{1c} 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 HbA_{1c} developed a global HbA_{1c} reference system with a much improved intra-assay and inter-assay coefficients of variation of <2.5%.[25 (Level II-1)]
  - For the purpose of diagnosis, the HbA_{1c} test should be performed using the method that is certified by the NGSP-HbA_{1c} units (%) and standardised according to the assays employed in the DCCT study. Recommendations have been made on the reporting of HbA_{1c} results as IFCC-HbA_{1c} values in SI units (mmol HbA_{1c}/mol Hb) [Refer to Section 3.8.1 and Table 3-21]

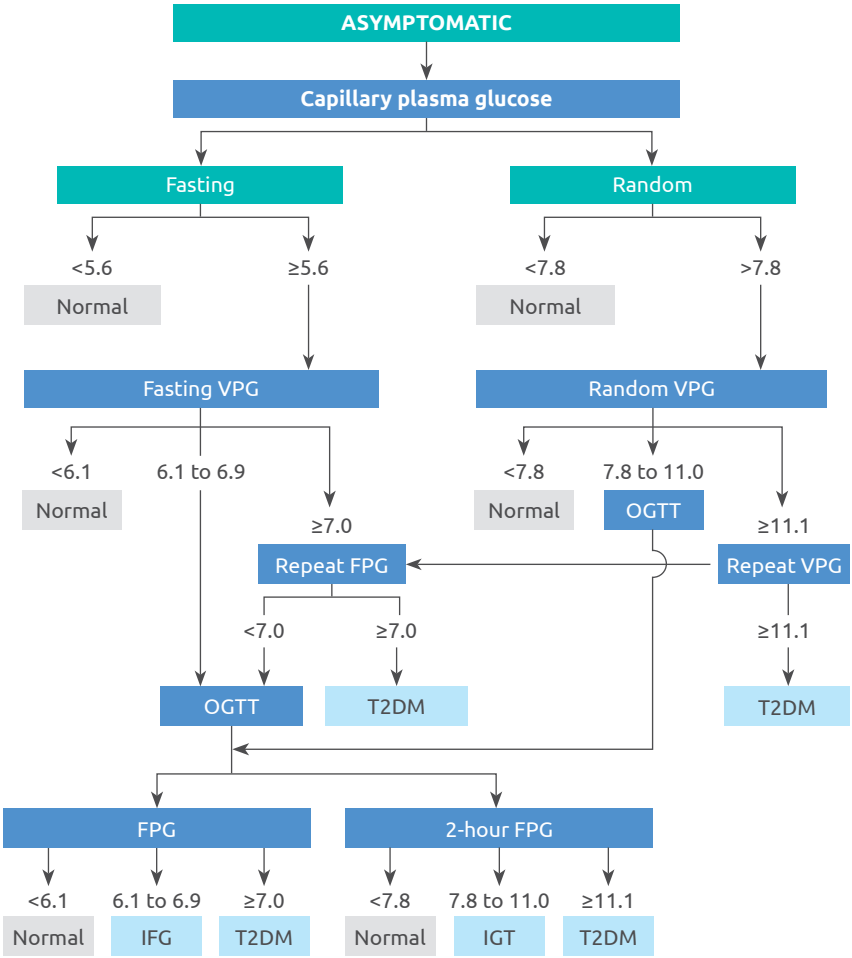
Figure 2-1: Screening for T2DM in symptomatic individuals



Screening of symptomatic individuals – A single abnormal VPG value or 1 abnormal HbA_{1c} is sufficient to make the diagnosis of T2DM.

T2DM: Type 2 diabetes mellitus; OGTT: oral glucose tolerance test. For diagnostic values based on OGTT, refer to Table 2-4.

Figure 2-2: Screening for T2DM in asymptomatic individuals



All glucose levels are in mmol/L.

Screening of asymptomatic individuals – Diagnosis of T2DM is made when there are 2 abnormal VPG on separate occasions or 1 abnormal VPG + 1 abnormal HbA_{1c} (from the same sample) values.

VPG: venous plasma glucose; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; T2DM: type 2 diabetes mellitus; PPG: post-prandial glucose; IGT: impaired glucose tolerance; IFG: impaired fasting glucose.

2.5 Cardiovascular risk estimation

- It is well established that patients with prediabetes and T2DM have a 2-3-fold increased risk of developing CVD.
- 60% of patients with T2DM will eventually die from CV complications.
- As such, it is prudent that the CV risk profiles be determined at diagnosis of prediabetes and T2DM as well as during each clinic visit.
- 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 FPG or HbA_{1c} should be performed annually in those with risk factors and those ≥30 years.	*Grade C*
2. Diagnosis of T2DM and prediabetes can be made using FPG or RPG, OGTT or HbA_{1c}.	*Grade B*
3. In individuals with a FPG of ≥6.1 to 6.9 mmol/L or HbA_{1c} between 5.7% to 6.2% further testing with a 75-g OGTT should be considered in order to categorise them into individuals with IGT or T2DM.	*Grade C*
4. Patients diagnosed with T2DM should have other CVD risk factors treated aggressively with close monitoring.	*Grade B*

SECTION 3

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

SUMMARY OF UPDATES

- Importance of categorizing patients at initial visit, in particular with regard to presence of co-morbidities; i.e. CV, renal complications, quality of life assessments, as it will help in deciding management plans.

3.1 Initial assessment

- At diagnosis of T2DM:
  - a detailed history which focuses on a few key issues which will affect treatment decision should be undertaken apart from assessing for symptoms and presentation of diabetes (Refer Table 3-1).[26]
  - full physical examination (including fundoscopy and monofilament test) and baseline investigations should be performed to assess for presence of ASCVD risk factors and complications of diabetes.
- Management is based on results of the above.[26]
- Diabetes management involves lifestyle modification, medications and patient education to encourage self-care and empowerment.[27,28 (Level I) 29,30 (Level III)]

Assessment

Table 3-1: Detailed assessment of a newly diagnosed patient with T2DM.

T2DM history	• Characteristics at onset (e.g. age, symptoms) • Increased thirst (polydipsia) • Polyphagia • Polyuria and/or nocturia • Malaise/fatigue • Weight loss/gain – some patients may gain weight and develop diabetes e.g. in Cushing's Syndrome. • Altered vision • Frequent and recurrent infections • Assessment of frequency/cause/severity of past hospitalisation • Assessment of history of macrovascular and microvascular complications: › ASCVD symptoms › neurological symptoms › visual disturbances › renal related symptoms › foot problems › sexual dysfunction • Screening for depression, anxiety and eating disorder • Identifying existing social barriers and support
Predisposition to T2DM	• Age over 30 years • Family history • Ethnic group • Overweight/obese • Lifestyle: › dietary habits › level of physical inactivity › smoking › alcohol consumption › occupation › sleep behaviour[31] • Hypertension • Dyslipidaemia • Obstetric history of large babies or gestational diabetes • Women with polycystic ovarian syndrome • Medications that impact weight and glycaemic status

Co-morbidities	• Non-alcoholic fatty liver disease (NAFLD) • Cognitive impairment/dementia • Obstructive sleep apnoea (OSA) • Pancreatitis • Periodontal disease • Low testosterone/hypogonadism in men • Cancers
Medications and vaccinations	• Review of treatment regimens and response (if defaulted previously) • Medication taking behaviour • Medication intolerance or side effects • Complementary and alternative medicine use • Vaccination status (influenza and pneumococcal vaccination)[32]
Referrals	• Annual dilated eye exam (Refer Section 5.1) • Family planning for women of reproductive age (if and when desired) • Registered dietitian for medical nutrition therapy (Refer Section 3.5.1) • Diabetes self-management education and support • Dentist for comprehensive dental and periodontal examination (Refer Section 5.9) • Mental health professional, if indicated (Refer Section 5.8) • Immunisation • Smoking cessation • Cancer screening
Risks affecting treatment decision and individualised target	• Atherosclerotic cardiovascular disease (ASCVD) • Heart failure • Renal impairment (Diabetic kidney disease; DKD) • Hypoglycaemia

Adapted from A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) 2019.[33 (Level III)]

Table 3-2: Physical examination of newly diagnosed patient with T2DM

Weight/waist measurement	• Body mass index (BMI) = weight (kg) / height^2 (m^2) • Waist circumference (WC) • Growth/pubertal development in adolescents
CV system	• Blood pressure (supine and standing) • Neck and peripheral pulses • Precordial examination
Eye (Refer Section 5.1)	• Visual acuity with refraction (with corrected vision) • Dilated retinal examination/photography (for retinopathy) • Cataract
Feet (Refer Section 5.6)	• Skin integrity • Pressure areas/callus formation • Ulcer • Toenails • Interdigital lesions • Foot deformities (structure/Charcot's joint) • Skin sensation • Pedal pulses (dorsalis pedis and posterior tibial)
Peripheral nerves (Refer Section 5.3)	• Tendon reflexes • Sensation: touch (e.g. with 10-g monofilament) • Vibration (e.g. with 128-Hz tuning fork)

Table 3-3: Investigations for a newly diagnosed patient with T2DM.

Baseline	• Fasting plasma glucose (FPG) • HbA_{1c} • Renal profile • Lipid profile • Liver function test • Urinalysis for albumin, microalbuminuria if albuminuria is absent • ECG

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.

Short-term aims

- Relief of symptoms and acute complications

Long-term aims

- Achievement of appropriate glycaemic levels with lifestyle management including weight reduction (where appropriate) and maintain durability of glycaemic control
- Reduction of other CV risk factors
- Identification and treatment of chronic complications
- Optimise quality of life

- Most of the microvascular complications of T2DM are related to the degree and the length of exposure to hyperglycaemia.[23,34 (Level I)]
- The legacy effect/metabolic memory of early glycaemic control is well established in reducing both micro- and macrovascular complications.[23,34 (Level I)] This should be emphasized in all patients with newly diagnosed T2DM.
- Multiple risk factor reduction (the ABC's for T2DM) has been shown to reduce long term complications and mortality sustained beyond the intervention phase.[35,36 (Level I)] These are:
  - A – Hb**A**$_{1c}$ (glycaemic control)
  - B – **BP** control
  - C – **Cholesterol** (lipid control)

3.2 Diabetes education

SUMMARY OF UPDATES

- Diabetes self-management education and support continues to be an essential part of ensuring patient motivation and adherence.
- Local primary healthcare diabetes education programs run as part of a chronic care model has been shown to be effective in improving glycaemic targets.
- Structured diabetes education programs that are patient-centred have been shown to improve glycaemic control; use of newer technology, e.g. digital web-based apps/short-messaging system (SMS) or phone calls further encourage patient participation.

- Diabetes education is effective in improving clinical outcomes and QoL[37-39 (Level I)] and their family members and carers should be involved as well.
- Diabetes education should be offered in a timely manner and suggested at four critical times for self-management education and support:[6,40-42 (Level III)]
  - at diagnosis,
  - annually,
  - when complicating factors arise; and
  - when transitions in care occur.
- Any member of the diabetes health team who has adequate training can deliver Diabetes Self-Management Education (DSME) with the physician as the head of team and coordinator.[42 (Level III)]
- The more the duration (frequency and length) of contact time between the educator and the patient, the better the HbA_{1c} reduction.[37 (Level II-1)]
- Provision of individual empowerment and self-management education strategies should be considered to enhance self-efficacy, self-care, self-management and motivation.[6,40,42-45 (Level III)]
- Structured diabetes education and support should be patient-centred, may be given in group or individual setting and/or using technology, for the purpose of improving self-management and self-empowerment.[6 (Level III)]
- Diabetes Self-Management Support (SMS)[6,40,42,45 (Level III)] 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 has been found to result in better outcomes.[46,47 (Level I) 48 (Level II-1)]
- Diabetes Education as part of the Chronic Care Model (CCM) has been shown to improve HbA_{1C} in primary healthcare clinic settings in Malaysia.
  - Incorporating diabetes education in the form of a structured and scheduled diabetes education program by a dedicated team, in a pragmatic, cluster-randomised, parallel, matched pair, controlled trial achieved significant HbA_{1C} of <6.5%, adjusted OR 2.16 (95% CI 1.34,3.50), p<0.002.[49 (Level II-2)]
- The design of a CCM's delivery system that incorporates diabetes education was reported to have the largest impact in improving patient outcomes (mean reduction of HbA_{1c} by 0.46% (95% CI 0.38, 0.54)[50 (Level I) 51,52 (Level II)] followed by CCMs that incorporate self-management support.[50 (Level I)]

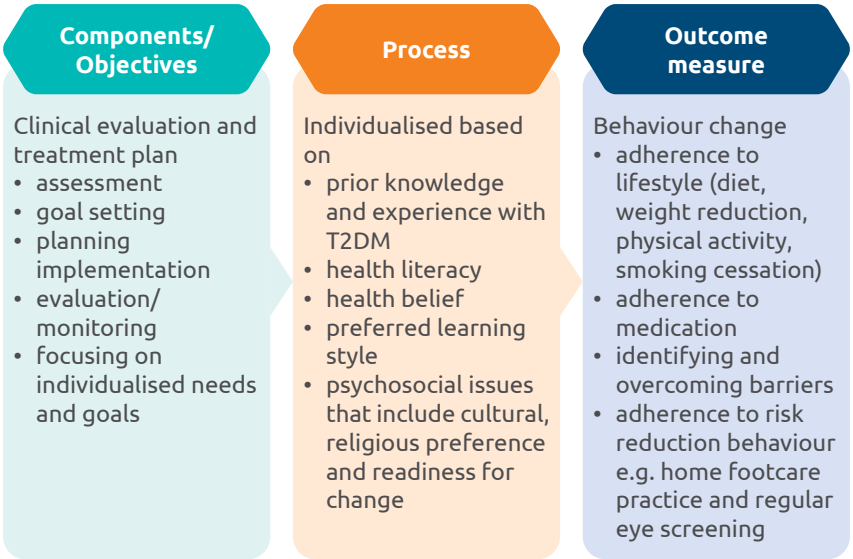
Table 3-4: Diabetes education

Scope of diabetes education	
• Self-Management Education › Diet › Food exchanges › Exercise › Medication › Complications (acute and chronic) › SMBG › Self-monitoring of BP and weight › Foot care › Smoking cessation › Problem solving skills e.g. management of hypoglycaemia, sick days › Psychosocial adaptation to diabetes e.g. to manage the stress associated with the initial diagnosis of diabetes or its complications and initiation of insulin	• Self-Management Support › Telephone contact › Digital/web-based/apps › Diabetes resource centres • Patient/Peer Support Organisation

Adapted from IDF Global Guideline for Type 2 Diabetes 2012,[53 (Level II-2)] DAA & ADEA Joint Position Statement 2009,[30 (Level II-2)] Boule N et al 2003,[54 (Level I)] Boule N et al 2001,[55 (Level I)] Skovlund S et al 2005,[56 (Level II-2)] Hill-Briggs F et al 2007,[57 (Level III)] Lustman P et al 2000.[58 (Level III)]

Figure 3-1: Process of Diabetes Self-Management Education (DSME)

Members of HCP team include: Diabetes educator, nurse, dietitian, doctor, pharmacist, health education officer, assistant medical officers and psychologist.



T2DM: type 2 diabetes mellitus. Adapted from American Association of Diabetes Educator. 2017.[59 (Level III)]

- Health education, diet therapy, exercise and adherence to medications must be reinforced regularly at every follow-up.[29,39 (Level I)]

3.3 Team approach

- Patient-centred comprehensive care requires a multi-disciplinary team of healthcare providers.
  - › Working with healthcare providers with different skills and specialities allows the patient to gain in-depth knowledge and understanding of their T2DM.[60 (Level III)]
  - › It also ensures that:
    - the patient's needs are addressed,
    - it avoids therapeutic inertia; and
    - it prioritises timely and appropriate intensification of lifestyle and/or pharmacologic therapy.

- 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 to ensure consistent advice and avoid confusing the patient.[60 (Level III)]

- Teams working together help patients to:[6,60 (Level III) 61 (Level II-2)]

  › get appropriate medical tests and examinations (e.g. plasma glucose level, BP, lipid level, weight, eye and foot examinations),
  › make healthy behaviour and lifestyle choices (e.g. improved diet, increased physical activity, cessation of smoking),
  › use medications to manage and control risk factors (e.g. plasma glucose, BP, lipids),
  › self-manage and adhere to treatment,
  › prevent diabetes-related complications,
  › improve QoL.

- Evidence[62-64 (Level II-2)] shows that these interventions are able to:

  › improve patients' glucose, BP and lipid levels,
  › increase proportion of patients who reach target plasma glucose, BP and lipid levels,
  › improve patients' diabetes related QoL and general physical, and mental health.

The following professionals are important team members in the multi-disciplinary management of T2DM.

Diabetes educator

- Diabetes nurse educators cover all topics related to T2DM management including knowledge, skills and health beliefs/perceptions regarding:

  › healthy eating,
  › physical activity,
  › self-monitoring,
  › medication usage, goal setting,
  › problem solving,
  › risk reduction practices such as foot care, smoking cessation and keeping follow-up medical appointments; and
  › healthy coping to assess presence of diabetes distress, anxiety and depression.

- They often have more time than doctors to allocate to each patient, which permits them to emphasize on specific needs.

Dietitian

- Referral to a dietitian is required to ensure detailed dietary education.
- Dietitians help patients develop healthful eating plans, appropriate to individual needs and circumstances.
- In addition, they can help identify and address problems such as disordered meal patterns, timing of meals, eating disorders and other physiological and psychosocial problems.
- These issues may not be readily identified during doctor office visits.
- The other team members also need to understand the principles of dietary advice to assist in reinforcing dietary recommendations (Refer Section 3.5.1).

Registered Nurses and Assistant Medical Officers

- Registered nurses and assistant medical officers can provide assessments before the doctor sees the patient, which allows for a better focus on any identified problems.
- Teaching medication administration is another important area that can be delegated to them.
- In addition, these healthcare providers can make follow-up phone calls to assess medication administration/adherence, medication tolerability, and other related diabetes management issues.

Physician/Endocrinologist/Diabetologist

- The advice of a specialist physician may be valuable for patients with complicated problems related to T2DM.
- These patients may present with poorly controlled diabetes 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' mode of 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 (Refer Section 5.1).

Oral health professional

- Dental and periodontal problems are common in patients with T2DM with a long established bi-directional influence reported.[65 (Level II-2)]
- People with T2DM tend to have poorer oral hygiene and more severe gingival and periodontal diseases[6 (Level III)] that:
  - › may contribute to worsening of glycaemic control;[61 (Level III) 66 (Level II-2)] and
  - › is a major cause of tooth loss, nutritional compromise, altered speech, low self-esteem and a poorer overall quality of life.[67 (Level II-2)]
- Therefore, referrals should be done routinely for oral healthcare (Refer Section 5.9).[68,69 (Level II-2) 70 (Level III)]

Recommendations: Assessment, aims of treatment and education

1. All newly diagnosed T2DM need to be reviewed by a medical doctor in which screening for other cardiovascular risks need to be carried out.	*Grade C*
2. The significance of the legacy effects/metabolic memory of good glucose control should be emphasized to all newly diagnosed diabetic patients.	*Grade A*
3. All patients should be referred for a formal diabetes education preferably delivered by a multidisciplinary healthcare professional team.	*Grade A*
4. The type of education, content, duration and revision frequencies will depend on needs of the patients and the resources available at the health care centre.	*Grade C*

3.4 Targets for control

SUMMARY OF UPDATES

- The importance of achieving optimal body weight with lifestyle modification is emphasized in overweight/obese T2DM individuals.
- HbA_{1c} targets: glycaemic targets have been revised according to individual characteristics.
- BP targets are revised to 130-139/70-79 mmHg.
- Lipid (LDL-C) targets according to CV risk i.e. moderate risk <2.6 mmol/L; high-risk <1.8 mmol/L; very high-risk <1.4 mmol/L (refer to Table 3-27).

Table 3-5: Targets for control

Parameters		Levels
Glycaemic control*	Fasting or pre-prandial	4.4 mmol/L-7.0 mmol/L
	Post-prandial	4.4 mmol/L-8.5 mmol/L**
	HbA_{1c}	<7.0% (for most) ≤6.5 %***
Lipids	Triglycerides	≤1.7 mmol/L
	HDL-C	Male: >1.0 mmol/L Female: >1.2 mmol/L
	LDL-C	≤2.6 mmol/L#
BP		≤130-139/70-79 mmHgˆˇ
Exercise		150 minutes/week
Body weight	If overweight or obese, aim for up to 10% weight loss in 6 months	

** Modified from the NICE guideline: Type 2 diabetes: The management of type 2 diabetes, 2014.[41 (Level III)] Glycaemic target should be individualised to minimise risk of hypoglycaemia.[71 (Level I)]*
*** Measured at least 90 minutes after meals.*
**** HbA_{1c} ≤6.5% is advocated for patients with a shorter duration of T2DM, no evidence of significant CVD and longer life expectancy, and have minimal risk of hypoglycaemia.*
 # In individuals with established CVD, LDL-C target is 1.4 mmol/L (Refer Table 3-26: LDL-C targets)
ˆ Target SBP to 130-139 mmHg - <130 mmHg if tolerated in individuals without pre-existing coronary heart disease and who are at higher risk of stroke or DKD, but not to <120 mmHg.
ˇ Target DBP to 70-79 mmHg, but not <70 mmHg.

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BP: blood pressure; CVD: cardiovascular disease; DKD: diabetic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Lipids: Refer Section 3.9.2; BP: Refer Section 3.9.1; Exercise: Refer Section 3.5.2; Body weight: Refer Sections 3.5.1 and 3.9.3.

Table 3-6: Individualised HbA_{1c} targets based on patient profile.

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed* • Younger age • Healthier (long life expectancy, no CVD complications) • On medications that do not cause hypoglycaemia • Albuminuria - nil • Low risk of hypoglycaemia	• All others	• Elderly patients • Presence of co-morbidities: › advanced CVD › coronary artery disease › heart failure › advanced renal failure (eGFR <45 ml/min/1.73 m^2) › decompensated chronic liver disease › dementia › bed-bound e.g. stroke/ other co-morbidities • Prone to/experiencing severe hypoglycaemia • Hypoglycaemia unawareness • High risk of consequence of hypoglycaemia such as: › those at risk of falling, › those who drive or operate machinery. • Those unlikely to benefit from strict glycaemic control • Short life expectancy

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus.
** Newly diagnosed is arbitrarily defined as T2DM <1-year duration and recently diagnosed is defined as T2DM duration of <5 years.*

Adapted from American Diabetes Association 2020; EASD 2019, NICE 2019 and Canadian 2018 guidelines.[6,40,43,72 (Level III)]

3.5 Lifestyle modification

SUMMARY OF UPDATES

- Medical nutrition therapy (MNT) with weight loss can prevent T2DM
- Structured lifestyle intervention incorporating partial diet replacement can improve HbA_{1c}, lipid profile and BP.
- A total diet replacement with weight loss of up to 15% body weight (approximately 15 kg) can lead to diabetes remission.
- A healthful eating pattern with low glycaemic index (GI) diet may be relevant in the Malaysian context because excessive rise in post-prandial glycaemia is frequently observed.

3.5.1 Medical nutrition therapy (MNT)

Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and delaying complications. Proper diet is crucial at all stages of management of diabetes including those on medication. The need for medical therapy should not be interpreted as a failure of lifestyle management but as an adjunct to it.

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 co-morbidities such as hyperlipidaemia, hypertension and DKD.[73] (Level I)
- Individualised dietary counselling by a dietitian is effective to lower HbA_{1c} up to 2.0% in 6 months, reduce weight, CV risk, lower medication use and improve quality of life (QoL).[6,74,75] (Level I)
- The goals of MNT are to:
  - › improve HbA_{1c}, BP, cholesterol levels, achieve and maintain body weight goals,
  - › promote healthful eating patterns in appropriate portion sizes and limiting food choices only when supported by scientific evidence,
  - › provide nutrition needs based on cultural preferences, health literacy and numeracy, willingness and ability to make behavioural changes.[73] (Level III)

Specific recommendations

A. Prevention of T2DM

The following diet and lifestyle changes are recommended for individuals with BMI >23 kg/m^2 (overweight) or >27.5 kg/m^2 (obese) who have prediabetes or are at risk for diabetes:

- Weight loss of ≥7%-10% of initial body weight within 6 months has been proven to be effective for diabetes prevention.[(Level I)] This can be achieved by:
  - reducing calorie intake of 500-1000 kcal/day from baseline[76 (Level I)] E.g. aim for intake of 1200-1500 kcal/day for women and 1500-1800 kcal/day for men,[77 (Level I)]
  - including ≥150 minutes/week of moderate to vigorous intensity physical activity e.g. 30 minutes of brisk walking for 5 days or more per week,[78 (Level I)]
  - a combination of reduced calorie diet, physical activity and behaviour modification can provide greater initial weight loss,[78 (Level I)]
  - using meal replacement plans (MRPs) as part of a structured meal plan for weight loss and weight maintenance.[79 (Level I)]
- A healthy dietary plan that includes:
  - a high fibre diet (20-30 g fibre/day) by choosing plant-based foods such as vegetables, fruits, legumes and whole grain cereals[80,81 (Level II-2)] has been shown to reduce risk of T2DM.
    - In several prospective cohort studies, a higher intake of vegetables, fruits, substituting white rice with brown rice and wholemeal bread may reduce risk of T2DM.[82-84 (Level II-2)]
    - Whole grains should form 50% of the total grain intake as recommended by the Malaysian Dietary Guidelines, 2020.[85 (Level III)]
  - avoiding consumption of sugar-sweetened beverages (SSB).[86 (Level II-2)] Replacing SSB with plain water has been shown to reduce risk of T2DM in a cohort study.[87 (Level II-2)]
  - a low fat intake to reduce body weight and improve glucose levels has been shown to be effective in several diabetes prevention RCTs.[88 (Level I)]
  - limiting intake of saturated fat, such as limiting red meat and processed meat consumption, has been shown to reduce risk of T2DM.[89 (Level II-2)]
  - following the Malaysian Healthy Plate Model may help increase consumption of vegetables and fruits and control portion size of meals.[90 (Level III)] (Refer Appendix 1)

B. Management of T2DM

- Weight management
  - › Individuals who are overweight (BMI >23.0 kg/m^2 - <27.5 kg/m^2) and obese (>27.5 kg/m^2) and not achieving glycaemic control should restrict their caloric intake with the goal of reducing body weight by at least 5%-10%.[(Level I)]
  - › Structured lifestyle intervention and:
    - MRP have been shown to be effective in lowering HbA_{1c}, lipid profile and BP.[91-94 (Level I)]
    - total diet replacement (TRP) (≤800 kcal/day) inducing weight loss up to 15% (approximately 15 kg) from baseline has been shown to lead to diabetes remission in T2DM patients.[95 (Level I)]
- Overall macronutrient distribution
  - › There is no ideal percentage of calories from carbohydrate (CHO), protein and fat for people with T2DM. A balanced diet consisting of 45%-60% of energy from CHO, 15%-20% energy from protein and 25%-35% energy from fat is encouraged.[96 (Level III)]
  - › These recommendations must be individualised based on weight, glycaemic and other metabolic goals, cultural preferences and individual lifestyle.

i. Amount and type of carbohydrates (CHO)

- Monitoring the total amount of CHO intake remains a key strategy in achieving glycaemic control.[97 (Level I)]
  - » Total amount of CHO intake can be monitored using grams, exchange list, household or hand measures as long as it is practical for patients to comprehend and follow.
  - » It is prudent to individualise the distribution of the total CHO exchanges allowed in a day into meals according to the patient's lifestyle. The current practical guide[98 (Level III)] is provided below:

Table 3-7: Guide to CHO exchanges for adult male and female.

Individuals	CHO exchanges (per meal)
Inactive women	2 to 4
Active women or inactive men	3 to 5
Active men	4 to 6
	CHO exchanges (snacks)
Between meal snacks	1 to 2

CHO: carbohydrate.

Adapted from American Dietetic Association Guide to Diabetes Medical Nutrition Therapy and Education; 2005.[98]

» CHO intake must be kept consistent on a day-to-day basis if the patient is on diet therapy alone, OGLDs or fixed insulin regime.[99 (Level I)]
» If the patient is adjusting their meal-time insulin doses or on insulin pump (i.e. flexible insulin dosing) consistency is not required. Insulin doses should be adjusted to match CHO intake. Self-monitoring of blood glucose (SMBG) is essential to adjust the insulin dose according to CHO intake.[100 (Level I)]

- 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.[101 (Level I)]
- CHO intake should emphasize nutrient-dense CHO sources that are high in fibre, including vegetables, fruits, legumes, whole grains, as well as dairy products.[96 (Level II-2)]
- Sucrose (e.g. table sugar) intake must be counted as part of the total CHO intake.[102 (Level III)] Excess sucrose intake contributes to calories and may cause weight gain.[103 (Level II-2)]
- Sugar substitutes (high-intensity sweeteners, artificial sweeteners, nonnutritive sweeteners, and low-calorie sweeteners) do not impact glycaemic level.[103,104 (Level II-2)]
  » These include saccharin, neotame, acesulfame-K, aspartame, sucralose, advantame, stevia, and luo han guo (or monk fruit).
  » Replacing added sugars with sugar substitutes will decrease daily intake of CHO and calories. Intake should not exceed acceptable daily intake (ADI) levels.
  » There is insufficient evidence that such sugar substitutes cause harm or increase the risk of diabetes.

ii. Glycaemic index

- GI is a measure to classify types of CHO based on their effect on plasma glucose level. It is a ranking system that indicates how quickly CHO foods raise plasma glucose level. Foods with high GI value raise plasma glucose more than food with medium or low GI.
- Substituting high GI foods with lower GI foods during meals reduces post-prandial plasma glucose (PPG), and modestly improves HbA_{1c} by (-)0.14%-(-)0.5%,[105-108 (Level I)] provided the energy and total CHO intake are not excessive. A lower GI diet may be relevant in the Malaysian context because excessive rise in PPG is frequently observed.
- Two recent systematic reviews regarding GI showed that studies which are longer than 12 weeks report no significant influence of glycaemic index or glycaemic load independent of weight loss on HbA_{1c}; however, mixed results have been reported for fasting glucose levels and endogenous insulin levels.[96,105,109 (Level I)] Further studies are needed to verify the benefits of low GI diets.

iii. Low CHO diets

- Reducing overall CHO intake for individuals with diabetes is not beneficial in the long-term. Benefits of lowering HbA_{1c}, triglycerides, promoting weight loss and lowering BP is only demonstrated in short-term studies of <6 months duration with a high risk of bias.[110 (Level I)]
  - » Changes in weight, lipid profiles and BP did not differ significantly between groups eating <40% energy (en) CHO vs. >40% en CHO.
  - » Long-term adherence and sustainability to a low-CHO eating plan is generally poor. In addition, there is variability in the definition of low CHO diet e.g. American Dietetic Association definition:
    - very low: <26% en CHO;
    - low: 26%-45% en CHO and
    - high CHO: >45% en CHO.

    The variability in definitions make studies' results difficult to interpret.
  - » A healthful eating pattern which is low in saturated fat, low in sodium, high in fruits and vegetables and wholegrain cereals will still need to be recommended when following a low-CHO diet.
  - » A very low CHO diet such as ketogenic diet (<50 g CHO) are discouraged due to challenges with long-term sustainability and nutrient imbalances of high fat content, excessive fibre intake and micronutrient deficiencies.[111 (Level III)] It is also unsafe for specific groups such as those with renal disease or disordered eating behaviours, and those taking SGLT2-i due to potential risk of ketoacidosis.[112,113 (Level III)]
  - » Meal plans that meet individualised caloric goals with a macronutrient distribution that is consistent with usual eating pattern is recommended for long-term achievement of glycaemia, lipids and weight goals.[113 (Level III)]

iv. Protein

- In patients with normal renal function, usual protein intake of 15%-20% energy has minimal effect on glycaemic control.[114 (Level I)]
- It is recommended to include lean sources of protein such as lean meat, fish, chicken/poultry without skin and soy protein.[114 (Level I)]
- In patients with impaired renal function, protein restriction of 0.8-1.0 g/kg body weight/day may be recommended.[115 (Level I)]

v. Fats

- Patients with T2DM should limit total fat (25%-35% energy intake), saturated fats (<7% energy intake) and minimise trans-fat (<1% energy intake) for prevention and treatment of CVD.[75,116 (Level I)]
- A healthy diet incorporating oats, nuts and legumes, green leafy vegetables and soy protein may be beneficial for cardiovascular health.[116 (Level I)]

- Sodium
  - 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 BP.[117 (Level I)]

- Dietary supplements and diabetes-specific formulas
  - Patients with T2DM 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, D, selenium, chromium, herbs and omega-3 fatty acids in improving glycaemic control.[118-120 (Level I)]
  - Diabetes-specific oral nutritional supplement (ONS) beverages or formulas may be prescribed for malnourished patients who are unable or have not been eating well for prolonged periods of time or these beverages are used as MRP for weight loss.[75 (Level III)]

- Intermittent fasting (IF) and time-restricted diets (TRE)
  - In IF, the eating period is restricted, with an unintentional reduction in calorie intake. TRE involves consuming all calories within a consistent 8 h-12 h daily timespan.
  - Due to limited evidence and small-scale studies, the effectiveness of IF and TRE in diabetes management is uncertain and not significantly different from conventional calorie-restricted diets.[121-124 (Level I)]

Refer to Appendices 2-4 on CHO foods, food exchange list and Glycaemic Index list.

Recommendations: Medical nutrition therapy

1. Medical nutritional therapy is the mainstay of prevention and treatment of T2DM. Proper diet is crucial at all stages of management of diabetes including those on medication.	*Grade A*
2. For obese and overweight patients, weight loss of up to 10% of initial body weight over a 6-month period is recommended to prevent T2DM.	*Grade A*
3. A healthful eating pattern i.e. low in saturated fat, low in sodium, high in fruits, vegetables, wholegrain cereals and legumes is recommended for prediabetes and T2DM patients.	*Grade B*
4. Meal plans that meet individualised caloric goals with a macronutrient distribution that is consistent with a healthful eating pattern is recommended for long-term achievement of glycaemia, lipids and weight goals.	*Grade B*

3.5.2 Physical activity

- Increased physical activity can improve glycaemic control, assist with weight maintenance, and reduce the risk of CVD.[55]
- Combining physical activity with dietary intervention results in greater HbA_{1c} reduction.
- Mild to moderate exercise is generally safe but before beginning a program of vigorous physical activity, people with T2DM should be assessed for complications that may preclude vigorous exercise (CVD, retinopathy, neuropathy and foot injury).[125 (Level II-2)]
- In older patients, previously sedentary, long-standing T2DM, patients with multiple risk factors, and patients with previous evidence of atherosclerotic disease should be considered for pre-exercise assessment (Refer Appendix 5). [(Level III)]
- 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.

- Individuals should exercise at least 3 times/week, preferably most days of the week and with no more than 48-72 hours without physical activity,[6 (Level III)] as the insulin-sensitising effect of an acute bout of exercise does not last beyond this duration[126 (Level II-2) 127,128 (Level III)] while, the improved insulin sensitivity of regular exercise training persists for up to 5 days after inactivity.[126 (Level II-2) 129 (Level I)]
- For patients with T2DM, supervised exercise programs have been particularly effective in improving glycaemic control, reducing the need for OGLDs and insulin, and producing modest but sustained weight loss.[130,131 (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 or at least 75 minutes/week of vigorous aerobic physical activity[125,132,133 (Level I)] and at least 2 sessions per week of resistance exercise[130 (Level I)] (Refer Appendix 6 for exercise examples).
- Greater reduction in HbA_{1c}[133 (Level I)] and CV complications[134 (Level II-2)] can be achieved with higher duration of exercise. It is therefore recommended to aim for a higher duration of exercise (300 minutes/week of moderate intensity) for those who are able to do so.
  - 0.9% mean HbA_{1c} reduction with >150 minutes/week vs. 0.4% reduction with moderate intensity exercise <150 minutes/week.
  - 20% reduction in CHD risk with 300 minutes/week vs. 14% risk reduction with moderate-intensity exercise 150 minutes/week.
- Duration of exercise should be increased to ≥60 minutes per day/ approximately 450 minutes per week in overweight or obese patients to facilitate weight reduction.[135 (Level III)]
- Any increase in daily energy expenditure is beneficial (Refer Appendix 6 for metabolic equivalent targets). [(Level III)]

There are many Malaysians with T2DM on basal bolus insulin regimen. There is limited data/evidence to guide recommendations for adjustment of glucose-lowering therapy in T2DM during exercise. The risk of hypoglycaemia with exercise in T2DM is much lower compared to patients with type 1 diabetes mellitus (T1DM).[136 (Level II-2)]

- However, risk of hypoglycaemia with exercise should still be considered in T2DM patients on SU therapy or insulin, as the hypoglycaemic effects of SU is increased with exercise[137 (Level II-2)] and a small number of individuals on insulin may develop hypoglycaemia with exercise.[138 (Level I)]

- Consideration of glycaemic pattern as part of individualised assessment is advised and treatment changes will depend on duration and intensity of the exercise, existing glucose-lowering therapy, any planned reduction in calorie intake as well as the prevailing glycaemic control and pre-existing rate of hypoglycaemia.[138 (Level I) 139,140 (Level II-1) 136 (Level II-2)]
  - Patients with suboptimal diabetes control (HbA_{1c} >7%) and known post-prandial hyperglycaemia without documented hypoglycaemia may not require any insulin dose reduction when commencing moderate-intensity exercise with usual diabetic diet.[140 (Level II-1) 136 (Level II-2)]
  - When combining initiation of exercise with reduction in calorie intake for weight-loss, there is a greater risk of hypoglycaemia. Reduction in glucose-lowering therapy with insulin, SUs and glinides should be considered depending on the baseline glucose profile. In T2DM patients with pre-existing symptomatic hypoglycaemia, reduction of such treatments by 50% or more should be considered prior to initiation of combination exercise and diet intervention.[138 (Level I)]
  - When there is concern about possibility of hypoglycaemia (patients with near-normal postprandial plasma glucose readings), reduction of bolus insulin of up to 50% (depending on exercise intensity) without adverse hyperglycaemia and exercise can also be performed in the postprandial state.[139 (Level II-1)]
  - Exercise performed in the fasting state may have greater impact on subsequent postprandial glucose reduction compared to exercise performed in the postprandial state.[141 (Level II-2)]
  - Elevated fasting plasma glucose in T2DM patients with dawn phenomenon, may be reduced by performing early morning exercise in the fasting state (prebreakfast).[142 (Level II-2)]
  - There is inadequate evidence to guide the need for glucose monitoring during exercise in T2DM patients. It is suggested that patients at high risk of hypoglycaemia (e.g. well-controlled diabetes on insulin therapy with calorie reduction) engaging in prolonged exercise (more than 30-45 minutes) should perform plasma glucose monitoring. This is based on experience with T1DM patients. [(Level III)]
- Hyperglycaemia is not a contraindication for exercise in people with T2DM provided they feel well (no symptoms of dehydration such as excessive thirst, nausea or fatigue).[143 (Level III)]

Recommendations: Physical activity

1. In older patients, previously sedentary, long-standing T2DM, patients with multiple risk factors, and patients with previous evidence of atherosclerotic disease should be considered for pre-exercise assessment.	*Grade C*
2. The duration of exercise should be at least 150 minutes/week of moderate-intensity and/or at least 75 minutes/week of vigorous aerobic and at least two sessions per week of resistance exercise.	*Grade A*
3. Higher duration of exercise (300 minutes/week of moderate-intensity) is advisable for greater benefit in glycaemic control and cardiovascular risk reduction.	*Grade B*
4. Glucose lowering drugs may need adjustment if exercise is planned. Insulin-treated patients engaging in moderate/high-intensity exercise may require counselling and modification of insulin doses.	*Grade C*

3.5.3 Tobacco cessation

- Smoking of tobacco and tobacco products (cigarette, electronic cigarette/vape, shisha, pipe, cigar etc.) can lead to various complications of chronic non-communicable diseases (NCD) such as coronary heart disease, cancers, and chronic lung disease. It is the main cause of death worldwide whereby 8 million people die every year as a consequence of this habit.[957]
- Hence, the decision to integrate smoking treatment with NCDs is important to reduce the prevalence of NCDs and their complications. This decision was made during the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) Steering Committee Meeting in December 2019 chaired by the Honourable Health Minister of Malaysia.
- The treatment for smoking should be initiated by the treating doctor based on the assessment and treatment of tobacco use disorder as in Appendix 12–Assessment and Treatment of Tobacco Use Disorder. More details on this can be found in the CPG on Treatment of Tobacco Use Disorder 2016, available at: *https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG_TobacoDisorder.pdf*

- Current evidence shows that T2DM individuals who smoke have a higher risk for cardiovascular morbidity and premature mortality and worse glycaemic control compared with T2DM non-smokers.[953 (Level II-3)]

3.6 Medications

SUMMARY OF UPDATES

- Recent cardiovascular outcome trials (CVOTs) have confirmed CV benefits beyond glucose lowering in 2 classes of GLDs i.e. GLP1-RA and SGLT2-i. As a result, a new paradigm shift in choice of drug therapy has emerged.
- Achieving HbA_{1c} targets remains an important goal that may require combining drugs that target the multiple pathophysiological defects.
- Recent evidence supports the use of early combination therapy for durability of glycaemic control.

3.6.1 Oral glucose lowering drugs (OGLDs)

Biguanides (Metformin)

- Metformin lowers blood glucose especially fasting plasma glucose by decreasing hepatic glucose production. It does not stimulate insulin secretion and as monotherapy, is usually not accompanied by hypoglycaemia.
- Metformin reduces HbA_{1c} by up to 1.5%.[144 (Level I)]
- Use in combination with other OGLDs has a synergistic effect to further reduce plasma glucose and may reduce insulin requirement.[145 (Level I)]
- Most common adverse effects are nausea, anorexia and diarrhoea.
  - These are minimised if metformin is taken together with/or after meals.
  - To reduce GI side effects, it is best to start with a single daily dose, followed by weekly titration.
  - Extended release formulation also reduces these side effects.[144 (Level I)]
- Vitamin B_{12} deficiency is a recognised uncommon long-term complication.[146 (Level II-2)]
- Lactic acidosis is rare (<1 case per 100,000 treated patients) and usually associated with renal impairment.[147 (Level I)]
- Metformin is weight neutral or may result in mild weight loss of up to 1.1 kg.[148 (Level II-1)]

- Doses beyond 2000 mg OD do not confer any further glycaemic benefit and significantly increase GI side effects.[145 (Level I)]
- Low dose metformin can be safely prescribed to lactating mothers.[149 (Level II-1) 150 (Level II-2)]

Table 3-8: Metformin formulations and dosages.

Drugs	Formulation (mg)	Dose	Maximum dose
Metformin	500 /1000	Initial dose: 500 mg OD	Usual: 1000 mg BD *Exception: 1000 mg TDS
Metformin SR	850	Usual dose: 850 mg BD	850 mg TDS
Metformin XR	500/750/1000	Initial dose: 500 mg OD Usual dose: 2000 mg OD	2000 mg OD

**Some patients may benefit up to a maximum dose of 1000 mg TDS.*
For fixed-dose combination formulations, please refer to Table 3-16 and specific product inserts. Dose escalation will depend on tolerability and according to the PI.
SR: slow release; XR: extended release; OD: daily; BD: twice daily; TDS: three times daily.

Sulphonylureas (SU)

- SUs reduce plasma glucose by increasing insulin secretion with an average HbA_{1c} reduction of 0.46%-1.62%.[151 (Level I)]
- The major adverse effect is hypoglycaemia.[151,152 (Level I)] The risk is higher in renal impairment, liver cirrhosis and the elderly.[153 (Level II-2)]
- Weight gain in the range of 1.31 kg-3.32 kg is common.[151,152 (Level I)]
- Among the second generation SUs, gliclazide, glipizide and glimepiride are preferred over other SUs as they cause less hypoglycaemia and less weight gain.[154,155 (Level I) 156 (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.[157 (Level III)]
- SUs are highly protein bound. Administration of drugs that can displace them (e.g. NSAIDs, anti-thyroid drugs, sulpha drugs, anticoagulants and α-blockers) can increase the risk of hypoglycaemia.[158 (Level III)]
- SUs should be taken 10-30 minutes before meals and can be combined with other OGLDs to improve glucose control.[158 (Level III)]
- The TOSCA IT, a multicentre, pragmatic trial, over 5.7 years, found the incidence of CV events was similar with SUs (predominantly glimepiride and gliclazide) vs. pioglitazone as add on treatment to metformin; with the conclusion that SUs and pioglitazone were equally safe with regard to CV risk.[159 (Level I)]

- In the recent CVOT (CAROLINA trial) of adults with T2DM and elevated CV risk, the head-to-head RCT comparing linagliptin (a DPP4-i) to SU (glimepiride), resulted in a non-inferior risk of a composite CV outcome. This study demonstrated non-inferior CV safety for linagliptin compared to glimepiride. This has eliminated the stigma of elevated CV risk previously associated with SUs.[160 (Level I)]

Table 3-9: SU formulations and dosage.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Glibenclamide	5	2.5 mg OD	10 mg BD
Gliclazide **Gliclazide MR**	80 60 /30	40 mg OM 30 mg OM	160 mg BD 120 mg OM
Glipizide	5	2.5 mg OM	10 mg BD
Glimepiride	2 /3	1 mg OM	6 mg OM

For fixed-dose combination formulations, please refer to specific product inserts. Dose escalation will depend on tolerability and according to the PI.
MR: modified release; OD: daily; OM: morning; BD: twice daily.

Note:
Glibenclamide is metabolised by the liver but its metabolites are active and excreted by the kidney. It is contraindicated in renal impairment. Other second-generation SUs (glimepiride, gliclazide and glipizide) may still be used in renal impairment with caution.

Refer to Appendix 7 for dose adjustment in renal impairment

Meglitinides

- These are short acting insulin secretagogues that bind to different sites within the SU receptor. It has a shorter half-life than SUs.[161 (Level I)]
- It should be taken within 10 minutes before main meals.
- It is primarily used to control PPG and reduces HbA_{1c} by 1.0%-1.2%.[161 (Level I)]
- It can be added to other OGLDs except SU.
- It is associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent.[148 (Level I)]

Table 3-10: Meglitinide formulation and dosage.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Repaglinide	0.5/1/2	0.5 mg with main meals	4 mg with main meals (not exceeding 16 mg daily)

Dose escalation will depend on tolerability and according to the PI.

Caution:
There is a higher risk of prolonged hypoglycaemia when repaglinide is combined with gemfibrozil.[162 (Level I)] This combination is contraindicated.

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.[163 (Level I)]
- It lowers PPG without causing hypoglycaemia and reduces HbA_{1c} by 0.5%-0.8%.[163 (Level I)]
- AGI significantly reduced risk of incident T2DM from IGT by 23%, whereas in those with IGT or T2DM, the impact on CV outcomes was neutral.[164,165 (Level I)]
- The common side effects are bloating, abdominal discomfort, diarrhoea and flatulence.[163,164 (Level I) 166 (Level II-1)]

Table 3-11: AGI formulation and dosage.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Acarbose	50/100	Initial dose: 50 mg OD Usual dose: 50-100 mg taken at 1st bite of main meals	100 mg TDS

Dose escalation will depend on tolerability and according to the PI.
OD: daily; TDS: three times daily.

Thiazolidinediones (TZD)

- TZDs are peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists and act primarily by increasing insulin sensitivity in muscle, adipose tissue and liver.
- TZDs reduce HbA_{1c} by 0.5%-1.4%.[167,168 (Level I)]
- Improvement in glycaemic control may only be seen after six weeks with maximum effect at six months.[169 (Level I)]
- Side effects include weight gain, fluid retention, heart failure, macular oedema and osteoporosis.[167,168,170,171 (Level I)]
- 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.[172 (Level I)]
- The use of lower dose may confer glycaemic efficacy while minimising risk of side effects.[173 (Level II-1)]
- TZDs are contraindicated in patients with CCF[170 (Level I)] and liver failure.

Table 3-12: TZD formulations and dosage.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Pioglitazone	15/30	15 mg OD	45 mg OD

Dose escalation will depend on tolerability and according to the PI.

Caution: *when used in combination with insulin due to risk of aggravating fluid retention.*[(Level III)]

OD: daily.

Incretins – Dipeptidyl peptidase 4 inhibitor (DPP4-i) and glucagon-like peptide-1 (GLP-1) analogue

- The incretin system has become an important target in the treatment of T2DM.
- After meals, incretins (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP])[174] (Level II-2) are released; these augment glucose-induced insulin secretion and suppress glucagon release thus reducing hepatic glucose output, and reducing plasma glucose in a glucose dependent manner.
- Incretins, at pharmacological levels, reduce gastric motility (thus slowing glucose absorption)[175] (Level II-2) and increase satiety by acting on centres in the brain.[176] (Level II-1)
- The incretin effect is markedly decreased in T2DM, resulting in delayed and reduced insulin release as well as lack of suppression of glucagon release after a meal.[177] (Level I)
- Agents that increase the effect of incretins have been proven to improve glucose control. 2 classes of drugs have recently been developed: DPP4-i (incretin enhancer) and GLP-1 analogue or GLP1-RA (incretin mimetic).[178,179] (Level I)

A. Dipeptidyl peptidase 4 inhibitor (DPP4-i)

- DPP4-i lower HbA_{1c} by 0.5%-0.8%.[180-185] (Level I)
- They are weight neutral and have a minimal risk of hypoglycaemia.[186-190] (Level I)
- DPP4-i CVOTs (CARMELINA, CAROLINA, TECOS, SAVOR-TIMI)[160,191-193] (Level I) have confirmed CV safety [Refer to Appendix 8 DPP4-i CVOT table].
- They are efficacious and safe in the elderly and all stages of DKD (See Appendix 7 for dose adjustment in renal failure).
- Saxagliptin is not recommended in patients with pre-existing heart failure[6] (Level III) as it has been shown to be associated with increased risk of hospital admission for heart failure.[193] (Level I)
- The VERIFY study has confirmed a delay in loss of glycaemic control when combination therapy (metformin + vildagliptin) is initiated within 24 months of diagnosis, as compared to sequential therapy.[194] (Level I)

Table 3-13: DPP4-i formulations and dosage.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Sitagliptin	25/50/100	25 mg OD	100 mg OD
Vildagliptin	50	50 mg OD	50 mg BD
Saxagliptin	2.5/5	2.5 mg OD	5 mg OD
Linagliptin	5	5 mg OD	5 mg OD

For fixed dose combination formulations, please refer to specific product inserts. Dose escalation will depend on tolerability and according to the PI.
OD: daily; BD: twice daily.

B. Glucagon-like peptide-1 receptor agonist (GLP1-RA) – will be discussed in Injectable therapies.

- Currently, all available GLP1-RAs are in the form of injectables.
- However, oral semaglutide may be made available in the near future.

Sodium-glucose Cotransporter 2 inhibitors (SGLT2-i)

- 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.[195-198 (Level I)]
- It reduces HbA_{1c} by 0.5%-1.0%.[199 (Level I)]
- Additional effects of treatment include weight loss (1.8 kg-2.7 kg) and reduction of SBP (2.7-4.8 mmHg) and DBP (1.8-2.0 mmHg). [199 (Level I)]
- It has a lower risk of hypoglycaemia, similar to placebo.[200 (Level I)]
- It can be combined with other OGLDs/GLP1-RA/insulin to improve glucose control.[(Level I)]
- SGLT2-i (EMPA-REG and CANVAS)[201,202 (Level I)] have been shown to significantly reduce MACE endpoints in T2DM with ASCVD [Refer to Appendix 8 SGLT2-i CVOT table].
- SGLT2-i have been proven to reduce hospitalisation for heart failure as a primary as well as secondary prevention (EMPA-REG, CANVAS and DECLARE-TIMI and VERTIS-CV).[203-205,952 (Level I)]
  - In two dedicated heart failure studies; (DAPA-HF)[206 (Level I)] and EMPEROR-Reduced[951 (Level I)] that included patients with heart failure with reduced ejection fraction (HFrEF), addition of SGLT2-i significantly reduced hospitalisation for heart failure and CV death by 25% (HR 0.75, 95% CI: 0.68-0.84, p<0.0001)[950] vs. placebo. These studies included patients with and without T2DM.

- Efficacy of glucose lowering effects of SGLT2-i are dependent on renal function and it is not recommended for glucose lowering, in patients with moderate to severe renal impairment.[207,208 (Level I)]
  - SGLT2-i reduce intraglomerular pressure independent of glucose levels.
  - A reduction of eGFR of approximately 5 ml/min/1.73 m^2 may occur in the first 1-3 months of starting an SGLT2-i.
  - SGLT2-i have been shown to be effective in reducing renal endpoints (reduction in macroalbuminuria, doubling of serum creatinine, ESKD and renal death) down to eGFR of 30 ml/min/1.73 m^2, in patients with DKD.[209 (Level I)]
  - Do not initiate at eGFR <30 ml/min/1.73 m^2 but, may continue if already initiated (see Section 5.2).
- Side effects of SGLT2-i include:
  - significant increase in urogenital mycotic infection and UTI;[202,207,210 (Level I)]
  - small but significant increase in risk of DKA, volume depletion[207,210 (Level I)] and osmotic diuresis;[211 (Level I)] and
  - cases of euglycaemic diabetic ketoacidosis (eDKA) have been reported in patients who were on SGLT2-i with inter-current illness (Refer to Section 4.3).[211 (Level I) 212 (Level III)]
- During inter-current illnesses/surgery, SGLT2-i may need to be withheld temporarily.[212 (Level III)]

Table 3-14: SGLT2-i formulations and dosages.

Drugs	Formulations (mg)	Minimum dose	Maximum dose
Dapagliflozin	5/10	5 mg OD	10 mg OD
Canagliflozin	100/300	100 mg OD	300 mg OD
Empagliflozin	10/25	10 mg OD	25 mg OD
Luseogliflozin	2.5/5	2.5 mg OD	5 mg OD
Ertugliflozin	5/15	5 mg OD	15 mg OD

For fixed dose combination formulations, please refer to Table 3-15. Dose escalation will depend on tolerability and according to the PI.
OD: daily.

Table 3-15: SGLT2-i fixed dose formulations and dosages.

Drugs	Formulation	Available dose (mg)	Maximum allowable dose
SGLT2-i + metformin			
Dapagliflozin	Dapagliflozin/ Metformin XR	5/500; 5/1000; 10/1000	10/2000 mg OD
Empagliflozin	Empagliflozin/ Metformin	5/500; 5/1000; 12.5/500; 12.5/1000	25/2000 mg divided dose
Ertugliflozin	Ertugliflozin/ Metformin HCl	2.5/850; 2.5/1000; 7.5/850; 7.5/1000	15/2000 mg divided dose
SGLT2-i + DPP4-i			
Dapagliflozin	Dapagliflozin/ Saxagliptin	10/5	10/5 mg OD
Empagliflozin	Empagliflozin/ Linagliptin	10/5; 25/5	25/5 mg OD
Ertugliflozin	Ertugliflozin/ Sitagliptin	5/100; 15/100	15/100 mg OD

Dose escalation will depend on tolerability and according to the PI.
OD: daily; XR: extended release; HCl: hydrochloride.

3.6.2 Injectable agents

Glucagon-like peptide-1 receptor agonist (GLP1-RA)[210,213,214]

- GLP-1 RAs currently available include exenatide IR and ER (once weekly), liraglutide (daily) and lixisenatide (daily) and, the once-weekly agents dulaglutide and semaglutide.
- GLP-1RAs have been shown to reduce HbA_{1C} (~0.8-1.6%), body weight (~1.0-4.1 kg). Their effects are dose dependent. The weight reduction is due to the effect on satiety and delay in gastric emptying.
- Common side effects of all GLP1-RAs are mainly gastro-intestinal i.e. nausea, vomiting and diarrhoea.[215 (Level I)]

A. Exenatide

- Exenatide formulations available: immediate release (IR) and extended release (ER) formulations.[208 (Level I)] Exenatide ER is the more commonly used preparation.
- Exenatide monotherapy results in a reduction of HbA_{1c} by 1.53%, comparable to metformin.[216 (Level I)]

- Exenatide ER,
  - › results in superior HbA_{1c} reduction, when compared to sitagliptin and pioglitazone as add on to metformin.[217 (Level I)] vs. sitagliptin and pioglitazone individually.[217 (Level I)]
  - › is significantly superior to basal insulin glargine as add on therapy to maximum OGLDs.[218 (Level I)]
  - › can be added on to SGLT2-i (dapagliflozin) for further HbA_{1c} reduction.[219 (Level I)]
  - › can be added on to existing basal insulin glargine therapy; with further HbA_{1c} reduction and significantly more patients reaching HbA_{1c} <7.0%.[220 (Level I)]
- Progressive weight loss is seen with its use.[221-223 (Level I)]
- In the EXSCEL study where Exenatide ER was compared to placebo in a high-risk population, the occurrence of primary MACE endpoints (death from CV causes, non-fatal MI or non-fatal stroke) did not significantly differ between the two groups [Refer to Appendix 8 GLP1-RA CVOT table].[224 (Level I)]

B. Liraglutide

- Liraglutide is indicated for use in combination with OGLDs and/or insulin. It results in reductions in mean HbA_{1c} of 0.8%-1.4%[225-228 (Level I)]
- There is no increased risk of hypoglycaemia and it may result in weight loss of up to 3.2 kg.[229 (Level I)]
- In patients who are on combination of metformin and SU with an HbA_{1c} <10.0%, the addition of liraglutide produced similar glycaemic improvement compared to insulin glargine without any increased risk of hypoglycaemia and weight gain.[225 (Level I)]
- In the LEADER study, MACE endpoints were significantly reduced in the liraglutide group vs. placebo [Refer to Appendix 8 GLP1-RA CVOT table].[230 (Level I)]

C. Lixisenatide

- Lixisenatide can be used in combination with OGLDs and/or basal insulin.[231,232 (Level I)]
- Monotherapy with lixisenatide results in a HbA_{1c} reduction of 0.5%-0.7%.[231,232 (Level I)]
- In Malaysia, lixisenatide is available as a fixed-ratio combination iGlarLixi which combines basal insulin glargine with prandial GLP-1RA lixisenatide.
  - › Once daily iGlarLixi was superior to iGlar monotherapy when used with metformin with or without a second OGLD and in patients inadequately controlled on basal insulin with or without OGLDs, with superior weight reduction.[233-235 (Level I)]

- Switching to iGlarLixi is superior to continuing maximally tolerated GLP-1 RA. Significantly more iGlarLixi patients achieve HbA_{1c} <7% compared to remaining on GLP1-RA alone.[236,237 (Level I)]

- Lixisenatide given to a very high-risk population with MI or hospitalisation for unstable angina and followed up for a mean of 25 months showed no significant difference in any components of the composite MACE endpoints [Refer to Appendix 8 GLP1-RA CVOT table].[238 (Level I)]

- Refer to package insert for dosing schedule.

D. Dulaglutide

- Dulaglutide is a long acting once weekly GLP1-RA.

- Dulaglutide:

  - monotherapy was slightly superior to metformin.[239 (Level I)]
  - as add-on to metformin, is superior to sitagliptin.[240,241 (Level I)]
  - can be combined with glimepiride for further significant HbA_{1c} reduction. [242 (Level I)]
  - can be added on to a SGLT2-i for further reduction in HbA_{1c} on a background of with or without metformin.[243 (Level I)]

- In comparison to other GLP1-RAs, dulaglutide showed:

  - similar efficacy in comparison to daily liraglutide. However, liraglutide demonstrated greater weight loss (3.6 kg vs. 2.9 kg).[244 (Level I)]
  - was significantly superior to exenatide BD with better HbA_{1c} reduction when added to OGLDs.[245 (Level I)]

- As add-on to insulin, addition of dulaglutide:

  - on a background of basal insulin glargine, resulted in significant further HbA_{1c} reduction;[246 (Level I)] and
  - on a background of prandial insulin, was superior to basal insulin glargine, with significantly greater HbA_{1c} reduction and a weight difference of 3.2 kg between groups.[247 (Level I)]

- In the REWIND study (over 5 years), which consisted predominantly of patients with CVD risk factors (70%), and established CVD (30%), dulaglutide was associated with a significant reduction of primary 3-point MACE endpoints [Refer to Appendix 8 GLP1-RA CVOT table]. [248 (Level I)]

E. Semaglutide

- Semaglutide is a once-weekly injectable human GLP-1RA (0.5 mg, 1 mg).

- It has a dose dependent effect on HbA_{1c} and weight reduction.[249 (Level I)]

- Semaglutide in both doses demonstrated superior glycaemic efficacy compared to:
  - › placebo in drug naïve patients.[250 (Level I)]
  - › sitagliptin on a background of metformin + TZD.[251 (Level I)]
  - › canagliflozin on a background of metformin.[252 (Level I)]
- Semaglutide can be effectively added on to SGLT2-i + existing OGLDs for further HbA_{1c} reduction.[253 (Level I)]
- Semaglutide is the most potent GLP1-RA with demonstrated superior glycaemic efficacy to exenatide ER, [254 (Level I)] dulaglutide[255 (Level I)] and liraglutide.[256 (Level I)]
- Semaglutide (both doses) has demonstrated superior glycaemic efficacy vs. basal insulin glargine, when added on to insulin naïve patients[257 (Level I)] or already on basal insulin glargine.[258 (Level I)]
- In the CVOT (SUSTAIN 6) over 104 weeks, semaglutide was associated with a significant reduction in risk of 3-point MACE [Refer to Appendix 8 GLP1-RA CVOT table].[259 (Level I)]
- Patients with a history of diabetic retinopathy should be monitored for progression of retinopathy and slower dose titration may be warranted[260 (Level I)] (Refer to Section 5.1).

Table 3-16: Summary of dosage, titration requirements, administration and actions in the event of a missed dose for GLP1-RA.

Drug	Titration	Initial dose	Recommended dose	Administration in relation to meals	Action if missed dose
Once daily					
Exenatide	Yes	5 µg BD for at least 1 month	5-10 µg BD	Should be administered within 60 min before main meals	Continue with the next scheduled dose
Liraglutide	Yes	0.6 mg OD for at least 1 week	1.2-1.8 mg OD	Any time without regard to meals	≤12 hrs: administer the dose as soon as possible >12 hrs: skip the dose
Lixisenatide	Yes	10 µg OD for 14 days	20 µg OD	Should be administered within 60 min before any meal	Administer the dose within 1 hr before the next meal

Once weekly					
Exenatide	No	N/A	2 mg once weekly	At any time without regard to meals	Administer the next dose as soon as practical. Only one injection should be administered in a 24-hr period
Dulaglutide	No	N/A	Monotherapy: 0.75 mg once weekly Add-on therapy: 1.5 mg once weekly	At any time, without regard to meals	≥3 days until the next scheduled dose: administer the dose as soon as possible <3 days: skip the dose, wait and administer their next regularly scheduled weekly dose
Semaglutide	Yes	0.25 mg once weekly for 4 weeks	0.5-1.0 mg once weekly (dose increase after 4 weeks if required)	At any time, without regard to meals	≥5 days until the next scheduled dose: administer the dose as soon as possible <5 days: skip the dose, wait and administer their next regularly scheduled weekly dose

Dose escalation will depend on tolerability and according to the PI.
For CV benefit refer to Appendix 8 GLP1-RA CVOT table.
µg: microgram; OD: daily; hr: hour.

Adapted from Romera I et al. Diab Ther 2018.[261]

Precautions for GLP1-RA

- They are not a substitute for insulin.
- Nausea and vomiting are common side effects and patients need to be adequately counselled.
- GLP1-RAs should not be combined with DPP4-i, as they both belong to the same class of incretins.
- They should not be used in patients with a history of pancreatitis.
- Should not be used in patients with a history of or a family history of MEN 2A or 2B or medullary thyroid cancer. [262 (Level II-1)]
- Exenatide and Lixisenatide should not be used in patients with gastroparesis.
- Refer to specific product inserts and Appendix 7 when treating patients with DKD.

Note:
When considering initiating GLP-1RA for CV risk reduction, we recommend choosing GLP-1RAs with proven CVD benefit[6 (Level III)] and has received label indication for CV benefit from NPRA.
For fixed ratio combination formulations, please refer to specific product inserts.

Table 3-17: GLP1-RA formulations and dosage.

Drugs	Formulations	Minimum dose	Maximum dose
Exenatide IR	5 µg/20 µL; 10 µg/40 µL	5 µg BD	10 µg BD
Exenatide ER	2 mg	2 mg weekly	2 mg weekly
Dulaglutide	0.75 mg/1.5 mg	0.75 mg weekly	1.5 mg weekly
Liraglutide	6 mg/mL	0.6 mg OD	1.8 mg OD
Lixisenatide	50 µg/mL; 100 µg/mL	10 µg OD	20 µg OD
Semaglutide	0.25 mg/0.5 mg	0.25 mg weekly	1.0 mg weekly

For fixed ratio formulations, please refer to specific product inserts. Dose escalation will depend on tolerability and according to the PI.
IR: immediate release; XR: extended release; µg: microgram; µL: microlitre; BD: twice daily; OD: daily.

3.6.3 General guidelines for use of oral glucose lowering drugs

- OGLDs can be used as monotherapy or in combination with other OGLDs, and/or injectable agents (e.g. insulin, GLP-RAs).

- Early combination therapy that addresses different pathophysiological defects in T2DM should be considered in the newly diagnosed T2DM patient.[194,263] (Level I)
  - › The VERIFY study has confirmed a delay in loss of glycaemic control when combination therapy (metformin + vildagliptin) is initiated within 24 months of diagnosis.[194] (Level I)
  - › Though these results have not been generalised to other OGLDs, it indicates the potential benefits of early combination therapy.
- 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.[264] (Level I) Other OGLDs are acceptable alternatives if metformin is not tolerated or contraindicated.
- If glycaemic targets are not achieved despite compliance, intensification of treatment should be made without delay.[6] (Level III)
  - › Barriers to medication taking should be addressed in patients with poor compliance.[6] (Level III)
  - › The medication regimen should be re-evaluated at regular intervals (3-6 months) and adjusted as needed to incorporate new patient factors such as:
    - ASCVD,
    - heart failure,
    - DKD,
    - hypoglycaemia event,
    - weight gain,
    - cost concern; and
    - change in socio-economic support.
- If monotherapy fails, combination of other agents is recommended.[265] (Level III)
- Compliance may be improved with daily dosing or fixed-dose combination (FDC) OGLDs.
- OGLDs are usually not the first-line therapy in stress hyperglycaemia. Insulin therapy is recommended.
- Targets for control should be individualised.
- There may be a role for de-escalation of OGLD doses/medication. Reasons for this include improvement in glycaemic control, successful weight loss (from lifestyle intervention), change in glycaemic goals (especially in the setting of elderly patients), development of new co-morbidities, development of intolerable side effects, or treatment ineffectiveness.[6] (Level III)

3.6.4 Combination of OGLDs, GLP-1RA and insulin

- If targets have not been reached after optimal OGLD therapy, consider adding:
  - pre-bed basal insulin,[266-270 (Level I)]
  - pre-dinner premixed insulin;[271,272 (Level I)] or
  - GLP-1RA, as an alternative to intermediate or long-acting insulin with less incidence of hypoglycaemia and weight gain.[218,257 (Level I)]
- Combining insulin with the following OGLDs/injectable agent has been shown to be effective:
  - Biguanide (metformin),[269,273,274 (Level I)]
  - Insulin secretagogue (SU),[275 (Level I)]
  - AGIs,[163,276 (Level I)]
  - DPP4-i,[277-279 (Level I)]
  - SGLT2-i,[195-198 (Level I)]
  - GLP1-RA,[210,229,232 (Level I)]
  - Insulin sensitizer (TZD)[280 (Level I)] – (combination of TZD and insulin is not generally recommended because of increased risk of fluid retention and congestive cardiac failure (CCF).
- Basal insulin dose should be increased until target FPG is achieved safely.
  - If HbA_{1c} targets are not achieved despite normal FPG, then PPG should be monitored.
  - If HbA_{1c} target is not achieved, further insulin intensification is required.
- In patients who are on insulin, metformin should be continued unless it is not tolerated or contraindicated.
- Even though glycaemic targets are important shared objectives (patient and HCP) due diligence should be given to progressive weight gain and exacerbation of insulin resistance (IR) especially those patients who are overweight and obese at start of therapy.
- Caution needs to be exercised when intensifying insulin dose/regimen with attention to weight gain and unrecognised hypoglycaemia.[281 (Level I)]

Recommendations: Combination of glucose lowering drugs

1. OGLDs can be used as monotherapy or in combination with other OGLDs, and/or injectable agents (e.g. insulin, GLP-1RA). Early combination therapy that addresses different pathophysiological defects in T2DM may be considered in recently diagnosed patients.	*Grade A*
2. As first line therapy, metformin is the preferred choice. Other OGLDs are acceptable alternatives, if metformin is not tolerated or contra-indicated.	*Grade A*
3. Medication regimen choice should address: a. co-morbidities such as ASCVD, heart failure and CKD; and b. risk for specific adverse drug effects, safety, and tolerability.	 *Grade A* *Grade C*
4. Cost of medications is a barrier and should be given due consideration when choosing treatment options.	*Grade C*
5. If targets are not met after optimal combined OGLDs therapy, consider adding GLP-1RA or insulin.	*Grade A*
6. HbA_{1c} remains an important target. If glycaemic targets are not achieved, intensification of treatment should be made every 3-6 months.	*Grade C*

3.6.5 Initiation, optimisation and intensification of insulin therapy

Adapted from Malaysian CPG on Insulin therapy in T2DM.[282 (Level III)]

- T2DM is a progressive disease characterised by worsening glycaemia due to progressive decline in beta cell function.[283 (Level I)]
- This ultimately renders OGLDs ineffective and the majority of patients with T2DM will require insulin therapy.
  - › Persistent hyperglycaemia in spite of optimal OGLDs and weight loss suggests beta cell failure.
  - › However, it is important to exclude concomitant illnesses such as; chronic infections, malignancy, 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 OGLDs or GLP-1RA.
- Insulin therapy should be considered in the following situations:
  - › inadequate glycaemic control on optimal dose and number of OGLDs[284 (Level I)] (Refer to Figure 3-2).
  - › as short-term use in the following;
    - acute illness or surgery,
    - pregnancy,
    - breast-feeding,
    - severe metabolic decompensation (e.g. diabetic ketoacidosis, hyperosmolar hyperglycaemic state).
  - › as initial therapy in newly diagnosed T2DM,
    - in presence of symptomatic hyperglycaemia and evidence of ongoing catabolism,[6 (Level III)]
    - when HbA_{1c} >10% or FPG >13.0 mmol/L;[6 (Level III)] or
    - as part of early insulinisation treatment regime.[285 (Level I) 286 (Level II-2)]

Insulin types and regimens

A. Insulin types

- The insulin currently used in this country are human insulin or insulin analogue. 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 through the night.

- **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.
- **Co-formulation insulin** is a combination of a rapid acting and basal insulin existing separately in one formulation. The basal and prandial components do not interact, and their distinct pharmacokinetic/pharmacodynamic profile are not compromised.

Table 3-18: Types of insulin and their pharmacokinetic profiles.

Insulin preparation	Onset of action	Peak action (hours)	Duration of action (hours)	Timing of administration of insulin
Prandial				
Short acting, Regular Actrapid Insugen R	30-60 min	2-4	6-10	30 min before meal
Rapid-acting Analogue Aspart (Novorapid) Lispro (Humalog) Glulisine (Apidra)	0-20 min	1-3	3-5	5-15 min before or immediately after meals
Basal				
Intermediate-acting, NPH Insulatard Insugen N	1-2 hour	4-8	8-12	Pre-breakfast/ Pre-bed
Long Acting Analogue				
Glargine U100 (Lantus, Basalog)	30-60 min	Less peak	16-24	Same time everyday
Glargine U300 (Toujeo)	Up to 6 hrs	Less peak	24-36	Once daily at any time of day, preferably at the same time within 3 hrs before/after usual time.
Detemir (Levemir)	30-60 min	Less peak	16-24	Same time everyday
Degludec (Tresiba)	30-90 min	Less peak	24-40	Flexible once daily injection (maximum interval up to 40 hrs)

Premixed insulins				
Mixtard 30	30 min	dual	18-23	30-60 min before meals
Insugen 30/70	30 min	dual	18-23	
Novomix 30	10-20 min	1-4	18-23	5-15 min before meals
Humalog mix 25/75	15 min	0.5-2.5	16-18	
Humalog mix 50/50	15 min	0.5-2.5	16-18	
Co-formulation				
IDegAsp 30 [Ryzodeg] Rapid-acting insulin analogue + basal insulin	10-20 min	1-4	24-40	5-15 min before meals

- The time course of action of different insulin preparations may vary in different individuals, or at different times in the same individual.
  - › The variations and time periods indicated in Table 3-18 should be considered as general guidelines only.
  - › The higher the dose of the insulin, the longer the duration of action.
- Long acting insulin analogues, which have less peak, result in lower hypoglycaemic episodes and less weight gain compared to human basal insulin.[267 (Level I)]
- Glargine U300 compared to Glargine U100 is non-inferior in achieving glycaemic control but with less overall and nocturnal hypoglycaemia.[287-291 (Level I)]
  - › The dose of Glargine U300 needed is generally 10%-17% higher compared to Glargine U100.[287-290 (Level I)]
- Premix/co-formulation insulins can be used to reduce the number of injections needed.
  - › Co-formulation insulin analogues (insulin degludec/insulin aspart) compared to premixed biphasic insulin aspart is non-inferior in HbA_{1C} reduction but with lower FPG and lower rate of confirmed nocturnal or overall hypoglycaemia.[292-294 (Level I)]

B. 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.
- The main advantage of insulin over other GLDs is that insulin lowers glucose in a dose-dependent manner to almost any glycaemic target. The main limitation of insulin is hypoglycaemia.

Initiation

- Insulin initiation can be done safely in an outpatient setting.
- Option for initiation include:
  - › basal insulin.[287-290 (Level I)]
    - can be initiated at 10U a day or 0.1-0.2 U/kg/day,
    - set FPG target and choose evidence-based titration algorithm e.g. increase by 2 U every 3 days to reach target FPG without hypoglycaemia; or
    - Adjust 2 U every week based on 3 days' glucose readings.
  - › Premixed insulin once or twice daily.
- All patients prescribed insulin therapy should be advised to perform self-monitoring of blood glucose (SMBG) and empowered to self-adjust their insulin doses (Refer to Section 3.8).
  - › Patients should be educated regarding symptoms of hypoglycaemia and its management.
  - › Insulin dose optimisation requires gradual, safe and prompt titration according to SMBG.[295 (Level I)]

Intensification

- After titration of basal insulin, if the HbA_{1C} is not at target but FPG is at target, intensification of insulin therapy, by adding prandial insulin or converting to premixed insulin is needed.
  - › Meta-analyses of trials comparing rapid acting insulin and human regular insulin in patients with T2DM have not reported important differences in HbA_{1C} or hypoglycaemia.[296,297 (Level I)]
  - › Insulin regimen intensification can be twice, thrice or four times (basal bolus) daily.
  - › Insulin pump may be considered in patients who are still not controlled while on basal-bolus regime.[298 (Level I)]

Barriers to insulin therapy

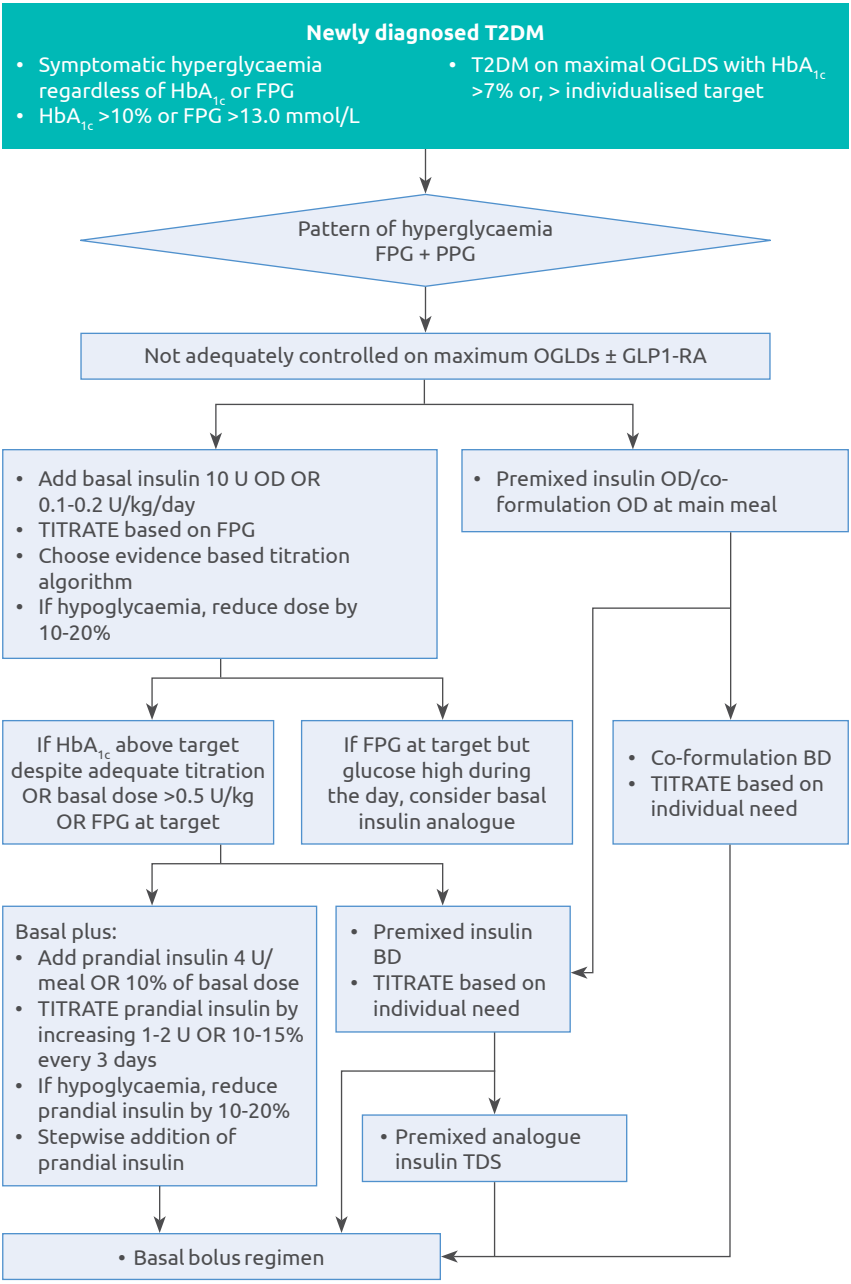
- There are numerous barriers to effective insulin therapy. These include patients and healthcare providers' factors e.g. non-adherence to insulin (missing/skipping doses), inappropriate reduction of insulin dose, wrong time of injections as well as fear of hypoglycaemia.
- The biggest barrier is adherence, and this should be adequately ascertained prior to any effort to intensify insulin therapy.[299] (Level II-3)

Table 3-19: Various insulin regimen options.

No. of injections/ day	Insulin regimen	Type of insulin and timing
1	Basal	Intermediate acting (NPH) insulin pre-bed
	Basal	Long-acting analogue once daily
	Premixed OD	Premixed/premixed analogue pre-dinner
	Co-formulations	Pre largest meal of the day
2	Basal	Intermediate acting (NPH) pre-breakfast and pre-dinner
	Premixed BD	Premixed insulin pre-breakfast and pre-dinner
	Basal + 1	Basal insulin OD + 1 prandial insulin
	Co-formulation OD + 1	1 co-formulation insulin pre main meal + 1 Prandial insulin pre-2nd main meal (no data in T2DM, data as in T1DM)
	Co-formulation BD	Co-formulation insulin pre 2 main meals
3	Basal + 2	Basal insulin OD + 2 prandial insulin
	Prandial	Prandial insulin pre-breakfast, pre-lunch and pre-dinner
	Premixed TDS	Premixed pre-breakfast, pre-lunch and pre-dinner
	Premixed BD + 1	Premixed insulin pre-breakfast and pre-dinner + 1 prandial insulin pre-lunch
	Premixed OD + 2	Prandial insulin pre-breakfast and pre-lunch + 1 premixed insulin pre-dinner
4	Basal bolus 1	Basal insulin OD + prandial insulin pre-breakfast, pre-lunch and pre-dinner
5	Basal bolus 2	Intermediate acting (NPH) insulin pre-breakfast and pre-bed + prandial insulin pre-breakfast, pre-lunch and pre-dinner

Table above describes variations of insulin regimens available depending on the number of injections/day and type of insulin with the timing.
OD: once daily; BD: twice daily; TDS: three times daily; NPH: Neutral Protamine Hagedorn; T1DM: type 1 diabetes mellitus.

Figure 3-2: Initiation and optimisation of insulin therapy.



T2DM: type 2 diabetes mellitus; FPG: fasting plasma glucose; PPG: post-prandial glucose; OGLDs: oral glucose lowering drugs; GLP1-RA: Glucagon-like peptide-1 receptor agonist; U: units; OD: daily; BD: twice daily; TDS: thrice daily.

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 (total daily dose >1.5 U/kg-2.0 U/kg) should prompt a search for an underlying cause/secondary problem such as:
  - non-adherence,
  - incorrect dosing, timing and injection technique (Available at Forum for injection technique guidelines, Malaysia at *http://mems.my/forum-for-injection-technique-malasyia-fit-my/*); and
  - occult infections.
- In general, total daily dose of prandial insulin should not be >50% of total daily dose.
- Patients should be encouraged to rotate their injection sites in the abdomen.
- Insulin therapy may cause weight gain through improved conservation of ingested calories, defensive eating from fear of hypoglycaemia or change in appetite regulation centrally.[281 (Level I)]
  - This effect is exaggerated if "unphysiological" dose of insulin is used.
  - Monitor weight – progressive weight gain should raise the possibility of too much insulinisation. Weight gain can be minimised by improving insulin sensitivity through diet, lifestyle measures or using insulin sensitizing OGLDs and, hence avoiding need for large doses of insulin.

3.6.6 Biosimilar insulin

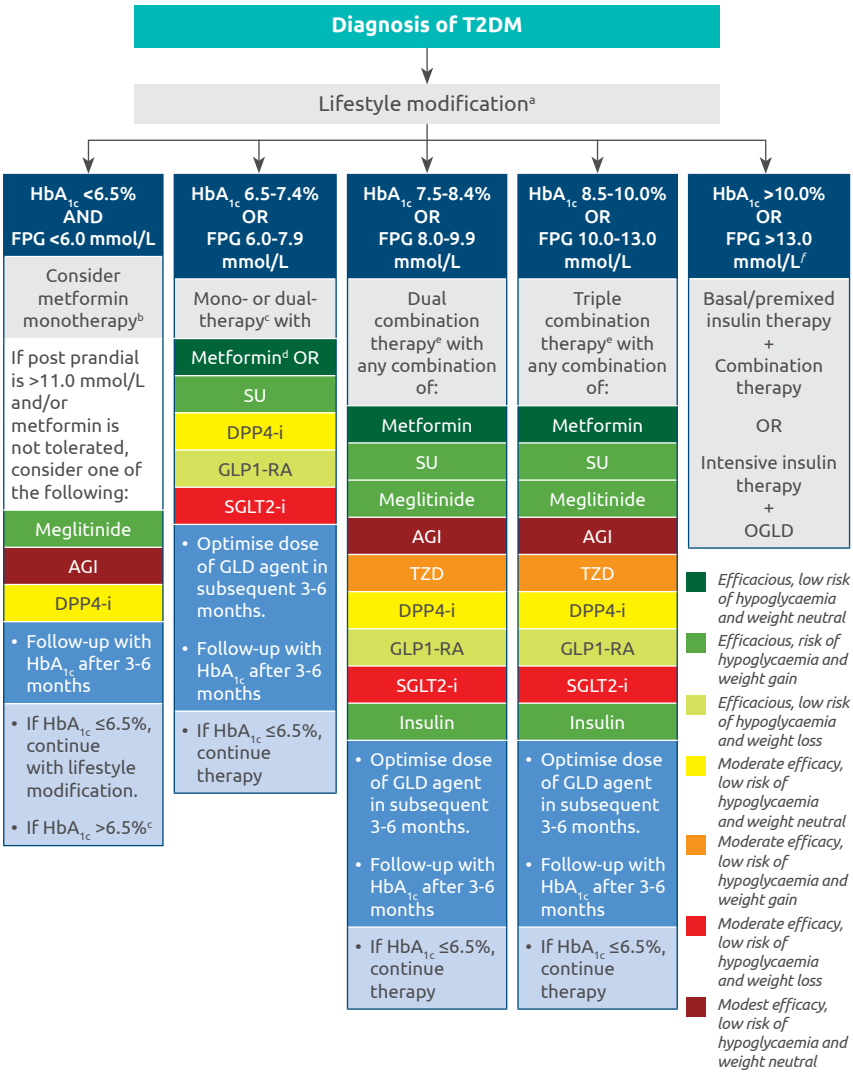
- Pharmaceutical companies other than the *original* multi-national ones also manufacture market-similar insulins.
- Because none of the insulin manufacturing processes are identical, this results in insulin that might become biosimilarly different from the originator insulin to a certain extent.[300]
- The National Pharmaceutical Regulatory Agency (NPRA) guidelines for market approval require that the manufacturer demonstrate that the insulin has a safety and efficacy profile that is similar to that of the *original* insulin formulation.
- Examples of available biosimilar insulins in Malaysia are Insugen-R, Insugen-N, Insugen-30/70, and Basalog (Glargine).
- Local post-marketing clinical studies have confirmed non-inferiority in efficacy and safety vs. original.[301]

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. OGLDs may be continued. SU may need to be reduced/stopped when intensifying insulin.	*Grade A*
3. The biggest barrier is adherence, and this should be adequately ascertained prior to any effort to intensify insulin therapy.	*Grade C*
4. Intensification of insulin therapy (i.e. increasing number of injections) should be considered if glycaemic targets are not met.	*Grade A*
5. Attention to weight gain, assessment for hunger/ defensive-eating behaviour and recognition of possibility of over-insulinisation is important. Lifestyle and dietary modification need to be emphasized at every stage of T2DM management.	*Grade C*

3.7 Treatment algorithms for the management of T2DM

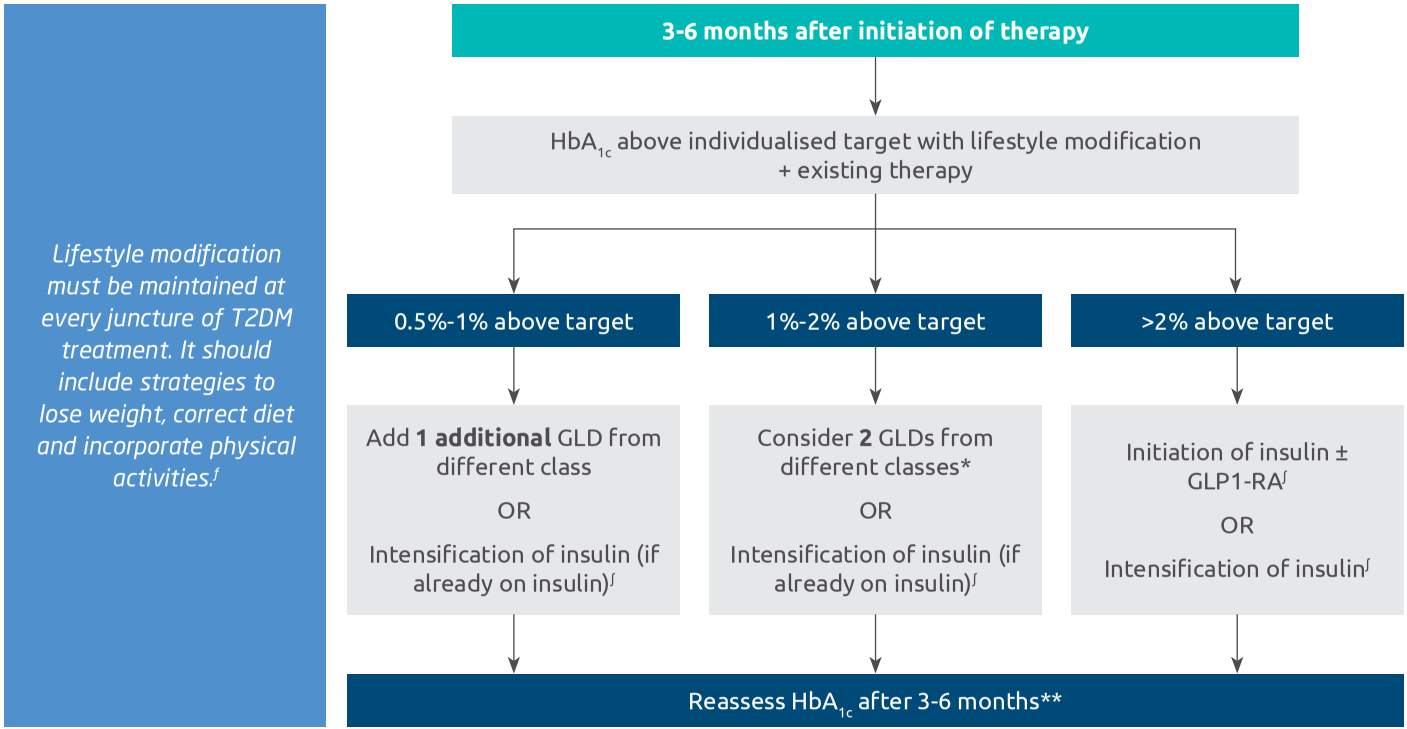
Figure 3-3: Treatment algorithm for newly diagnosed T2DM



a. Lifestyle modification: refer to Sections 3.5.1 and 3.5.3. b. If patients are able to normalise plasma glucose (glucose profile/HbA_{1c}) and/or lose weight, may continue metformin. c. Consider addition of DPP4-i (vildagliptin) – In the VERIFY trial metformin + vildagliptin delays loss of glycaemic control when initiated within 24 months of diagnosis.[194 (Level I)] d. Meglitinide/AGI/TZD may not be appropriate for monotherapy. e. Combination therapy includes both oral and injectable (GLP1-RA) GLD. f. For patients who are symptomatic refer to Section 3.6.5.

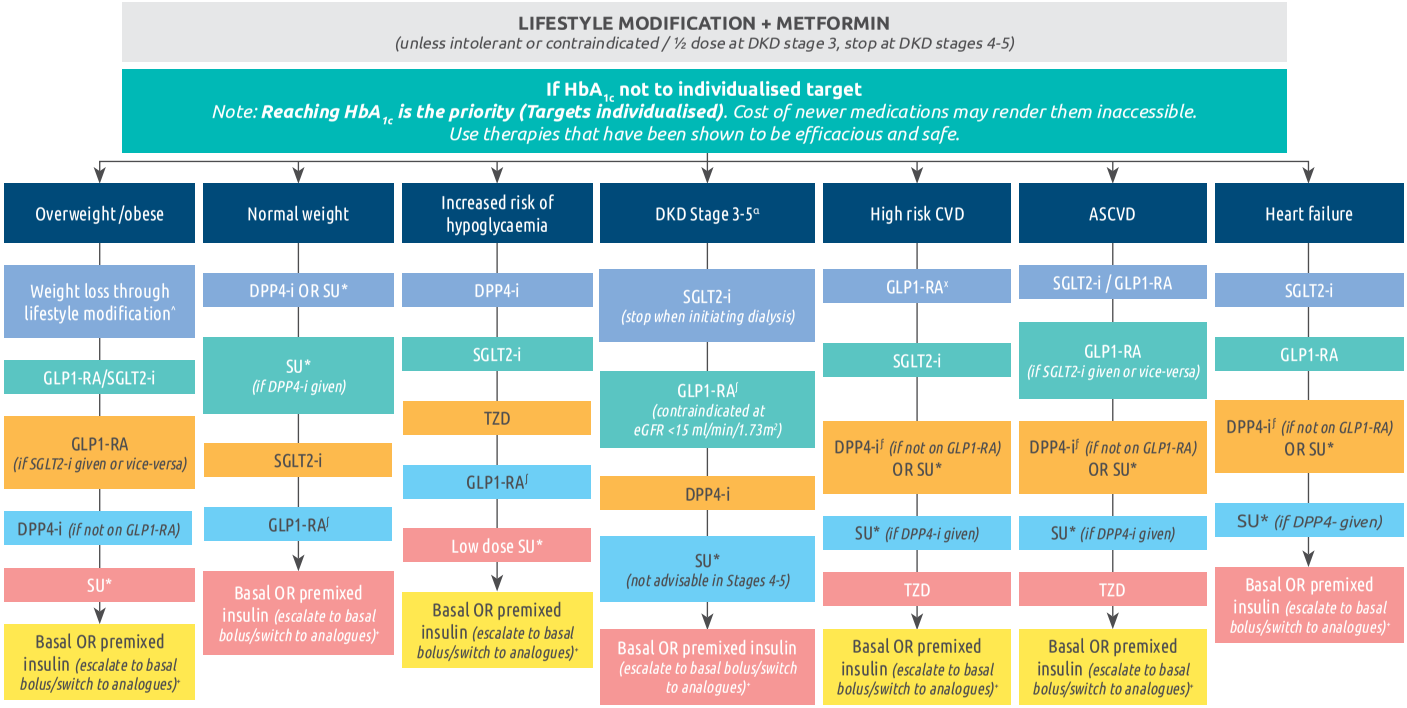
FPG: fasting plasma glucose; AGI: alpha-glucosidase inhibitors; DPP4-i: dipeptidyl peptidase-4 inhibitors; SGLT2-i: sodium-glucose cotransporter 2-inhibitors; SU: sulphonylurea; GLP1-RA: glucagon-like peptide-1 receptor agonist; TZD: thiazolidinediones; GLD: glucose lowering drugs; OGLD: oral glucose lowering drugs.

Figure 3-4: Treatment recommendations for patients with T2DM on clinic follow-up.



** Maximum OGLDs allowed is 5. [f] When on insulin continue metformin/SGLT2-i/DPP4-i/GLP1-RA. Stop SU if on full insulin. [f] Lifestyle modification: refer to Sections 3.5.1 and 3.5.3. ** for GLDs – interval before addition of another GLD may need to allow for dose titration and escalation of the current therapy. DPP4-i: dipeptidyl peptidase-4 inhibitors; SGLT2-i: sodium-glucose cotransporter 2-inhibitors; SU: sulphonylurea; GLP1-RA: glucagon-like peptide-1 receptor agonist; GLD: glucose lowering drugs.*

Figure 3-5: Suggested treatment approach for specific patient profiles.



*1. Patients who are well-controlled on their existing therapies should continue with the treatment regime. 2. Bariatric surgery may be considered in patients with BMI ≥32 kg/m² and their T2DM cannot be controlled by lifestyle changes and pharmacotherapy. CVD divided into 2 categories: ASCVD – established atherosclerotic cardiovascular disease (ASCVD) / High risk CVD – Primary Prevention, without clinical CV events. ^ VLCD + MR P- Refer to Section 3.5.1; * SU refers to 2nd generation sulphonylurea; [f] Stop DPP4-i; [j] Saxagliptin (SAVOR-TIMI) showed increased risk of hospitalisation for heart failure. [x] Choose GLP1-RA with proven CV benefit and has appropriate label indication for CV reduction; [a] SGLT2i recommended in DKD stage 3-5 – for renoprotective effects, do not initiate when <30 ml/min/1.73m²; however, eGFR levels at which SGLT2-i can be initiated may be subject to change as new evidence become available, + may switch to basal-bolus human/analogue insulin where appropriate; for hypoglycaemic risk - insulin analogue may be more appropriate. DPP4-i: dipeptidyl peptidase-4 inhibitors; SGLT2-i: sodium-glucose cotransporter 2-inhibitors; SU: sulphonylurea; GLP1-RA: glucagon-like peptide-1 receptor agonist; TZD: thiazolidinediones; VLCD: very low-calorie diet; MRP: meal replacement therapy.*

Figure 3-6: Efficacy of various GLDs.

	MET[144] (Level I)	SU[151,154,155] (Level I) 156 (Level II) 157 (Level I)	GLN[161] (Level I)	AGI[163] (Level I)	TZD [167-172,302,303] (Level I)	DPP4-i 160,180-193 (Level I)	SGLT2-i 199,201-209, 955 (Level I)	GLP1-RA 120,213,214 (Level I)	Insulin [268,291, 292,304] (Level I)
HbA_{1c} ↓ %	1.0-1.5	0.4-1.6	1.0-1.2	0.5-0.8	0.5-1.4	0.5-0.8	0.2-0.8	0.5-1.4	>1.5
FPG vs. PPG	FPG	Both	PPG	PPG	FPG	Both	Both	Both	Both
Hypoglycaemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓–↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
CHF	↔	↔	↔	↔	↑	↔	↓↓	↔	↔
CVD	↓	↔	↔	↔	↔	↔	↓↓	↓↓	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
DKD	Avoid*	Hypo	Hypo	↔	Fluid ret'n	Dose adjustment	↓↓[a]	↓[†]	Hypo

Increased risk *Mild-mod risk* *Neutral* *Possible benefit* *Beneficial*

** Avoid if eGFR < 30ml/min/1.73m²; †avoid if eGFR < 15 ml/min/1.73m²; ªSGLT2-i can be used until dialysis is initiated and has proven reno-protection although glucose-lowering efficacy is reduced.*

3.8 Monitoring

SUMMARY OF UPDATES

- Self-monitoring of blood glucose (SMBG)
  - SMBG is important in people with insulin treated T2DM.
  - SMBG may improve glycaemic control in people with non-insulin treated T2DM with short diabetes duration, HbA_{1c} ≥8% and/or obesity.
  - Mobile health may promote diabetes self-management, although more evidence on application (apps) accuracy, data security, accessibility and sustainability are required.
- Continuous glucose monitoring (CGM)
  - CGM technology has evolved significantly in recent years with emerging evidence as a useful tool in glycaemic monitoring in people with T2DM.
  - Ambulatory glucose profile and key glucose metrics derived from CGM reports provide objective insights into individual glycaemic variability that facilitate improved glycaemic management and promote self-engagement.

3.8.1 Glycated haemoglobin (HbA_{1c})

- HbA_{1c} assay must be standardised to the National Glycohemoglobin Standardization Program (NGSP).
  - NGSP results can be directly correlated with clinical outcomes especially DCCT[305 (Level I)] and UKPDS[306 (Level I)] trials and therefore, the decision by most guidelines to utilise HbA_{1c} for diabetes care goals and targets (NGSP website is available at *http://www.ngsp.org/*).[307 (Level III)]
- The assay quality has been improved and calibrated via the International Federation of Clinical Chemistry (IFCC). But, IFCC results are more accuracy-based via latest and newer assay techniques (Conversion between NGSP and IFCC is available at *http://www.ngsp.org/convert1.asp*).[307 (Level III)]
- Correlation between IFCC and NGSP is good, but the absolute numbers are different. IFCC HbA_{1c} results are consistently 1.5-2.0% lower than NGSP HbA_{1c} results. NGSP HbA_{1c} is reported as % while IFCC HbA_{1c} is now reported as mmol HbA_{1c}/mol Hb.[307 (Level III)]

Table 3-20: Relationships between NGSP, IFCC HbA_{1c} and estimated average glucose (eAG).

NGSP HbA_{1c} (%)	IFCC HbA_{1c} (mmol/mol)	eAG (mmol/L) (95% CI)
5.0	31	5.4 (4.2-6.7)
6.0	42	7.0 (5.5-8.5)
7.0	53	8.6 (6.8-10.3)
8.0	64	10.2 (8.1-12.1)
9.0	75	11.8 (9.4-13.9)
10.0	86	13.4 (10.7-15.7)
11.0	97	14.9 (12.0-17.5)
12.0	108	16.5 (13.3-19.3)

Calculator for converting HbA_{1c} results into estimated average glucose (eAG) is available at https://professional.diabetes.org/diapro/glucose_calc. Master equation to interchange NGSP and IFCC values is available as well. NGSP: National Glycohemoglobin Standardization Program; IFCC: International Federation of Clinical Chemistry.

Adapted from Nathan DM et al 2008,[308(Level II-1)] NGSP website.[307 (Level III)]

- Depending on the country and laboratory, HbA_{1c} results may be reported as % (NGSP), mmol/mol which is mmol of HbA_{1c}/mol of haemoglobin (IFCC) or estimated average glucose (eAG) as mmol/L. It can also be a combination of any of the 3.
- In adults with T2DM, HbA_{1c} can be measured at:[72 (Level III)]
  - 3-6 monthly intervals, until the HbA_{1c} is stable on unchanging therapy,
  - 6 monthly intervals once the HbA_{1c} level and glucose-lowering therapy is stable.
- HbA_{1c} has a strong predictive value for diabetes complications.
  - Reduction in HbA_{1c} will result in a reduction in risk of microvascular complications in the immediate short-term[24 (Level I)] and macrovascular complications in the long-term.[24,309,310 (Level I)]
- HbA_{1c} target should be individualised.
  - Therapy in most patients with T2DM should be targeted to achieve HbA_{1c} ≤7.0%.
  - A more aggressive target (≤6.5%) should be attempted in those with long life-expectancy, no co-morbidities and in those whose targets can be achieved without causing severe hypoglycaemia (Refer to Table 3-6).
- Despite the standardisation, sometimes the measured HbA_{1c} value may still at times not reflect the true level of glycaemia (glycation gap) due to various causes. [18 (Level I) 19 (Level III)]

Table 3-21: Causes that may affect the HbA_{1c} value.

Higher HbA_{1c} values	Lower HbA_{1c} values	Either higher or lower HbA_{1c} values
• Rapidly improved diabetes • Age (older) • Iron deficiency • Vitamin B_{12} deficiency • Folate deficiency • Hypothyroidism • Vitamin E supplementation	• Sudden onset or exacerbation of diabetes • Period of recovery from iron deficiency anaemia • Hemolysis • Blood loss/ transfusion • Renal anaemia during treatment with erythropoietin • Liver cirrhosis • Asplenia • Treatment with iron • Treatment with B_{12} • Treatment with folate	• Haemoglobinopathy (depends on the type of assay and type of haemoglobin variant) • Ethnicity (Indian and Malays – higher values, Chinese – lower values)[311 (Level II-2)] • Medications: Dapsone

Adapted from Campbell L et al 2019,[18 (Level I)] Japanese Diabetes Society 2016-2017.[19 (Level III)]

- For haemoglobin variants, NGSP via their website has published a list of HbA_{1c} methods and any possible interference (This is available at *http://www.ngsp.org/interf.asp*.
- Recognise the occurrence of a possible glycation gap and in what circumstances these may occur. Other methods of measuring glycaemia in these situations should be considered, as listed below:[41 (Level III)]
  - SMBG / preferably quality controlled capillary glucose profiles – this is the most ideal/practical method; or
  - total glycated haemoglobin estimation (if abnormal haemoglobins) using boronate affinity methods. These are available in select hospitals.
- Other limitations of HbA_{1c} are that it does not provide information on glucose variability and does not capture hypoglycaemia. In such circumstances, a combination of SMBG and HbA_{1c} is appropriate.

Fructosamine estimation

- The evidence that correlates fructosamine to average glucose levels and its prognostic significance are not as strong as HbA_{1c}.[312 (Level III)]
- It is an alternative to HbA_{1c} in monitoring glycaemic control in patients in whom HbA_{1c} measurements may be inaccurate.
- It only reflects glycaemic control over the recent 2-3 weeks.

Point of care testing

- Point of care (POC) devices should not be used for diagnosis of T2DM.[313 (Level I)]
- However, POC devices are gaining popularity.
  - › POC devices fill an unmet need – making HbA_{1c} assessment possible in the more remote/interior regions of the country where laboratory facilities are not readily available.
- Initial devices tended to underestimate HbA_{1c} (i.e. below lab-based levels by -0.962 to +0.1). But this negative bias has been improved by more recent POC devices (+0.28 to +0.43).[313 (Level I)]
- This degree of imprecision may adversely affect management decision.
- As precision and accuracy in newer POC devices continue to improve, they have the potential to be as accurate as laboratory based HbA_{1c}. This can reduce cost, waiting time and necessity for multiple visits, improve QoL, and increase accessibility to remote/interior areas and also for the paediatric population (minimal blood needed).
- The main utility for POC devices will be in the monitoring of diabetes management in follow-up of patients.

3.8.2 Self-monitoring of blood glucose (SMBG)

- 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 treated with insulin[(Level 1)] and is desirable for those on OGLDs.[6(Level III)]

In out-patient setting

- Insulin treated T2DM
  - › Recommend routine SMBG to evaluate glycaemic control and prevent hypoglycaemia.[(Level I)]
  - › Frequency and timing of SMBG vary based on types of insulin regimen (Refer Section 3.6.5).[6]

- Non-insulin treated T2DM
  - › Earlier RCTs and meta-analyses suggest lack of benefit with SMBG in this group.[314 (Level I) 315 (Level II)]
  - › However, recent meta-analyses and RCTs suggest that SMBG could modestly reduce HbA_{1c} by 0.12%-0.33%, especially in those with:[316-322 (Level I)]
    - short duration of diabetes,
    - suboptimal glycaemic control (baseline HbA_{1c} ≥8%),
    - obesity (BMI ≥30 kg/m^2).
  - › Greater glycaemic improvements were reported with:[316-319,322,323 (Level I)]
    - more frequent SMBG,
    - high levels of health literacy,
    - structured SMBG and evaluation of technique with regular feedback*,
    - adjustment of therapy (diet, physical activity and GLDs).**

**By health care providers (clinicians, diabetes-skilled allied health personnel).*
*** By patients themselves with emphasis on self-management support and on-going patient empowerment by health care providers.[316,323]*

Frequency and timing of SMBG

- Frequency and timing of SMBG should be tailored based on the patient's needs including glycaemic status, drug therapy, treatment goals and lifestyle (dietary patterns and level of physical activity).[(Level II-2)]
- Re-evaluation of the need for and frequency of SMBG should be performed by healthcare providers during each follow-up visit.[(Level II-2)]
- Ideally, SMBG should be performed on a daily basis in people with insulin-treated T2DM or if possible, at least one 24-hour cycle on a weekly basis. [(Level II-2)]

Table 3-22: Recommendations for SMBG.

Mode of Treatment	Breakfast		Lunch		Dinner	
	Pre	Post	Pre	Post	Pre	Post / Pre-bed
Diet only	√	√	-	√	-	√
OGLDs	√	√	-	√	-	√
Insulin	√	√	√	√	√	√

OGLDs: oral glucose-lowering drugs.

- Glucose monitoring in relation to different insulin regime.
  - › Once pre-prandial glucose levels are achieved, postprandial (PPG) testing is recommended for fine adjustment of insulin dosage, taking into account the effect of diet and physical activity levels.[(Level III)]

Figure 3-7: OGLDs + bedtime insulin-intermediate acting insulin.

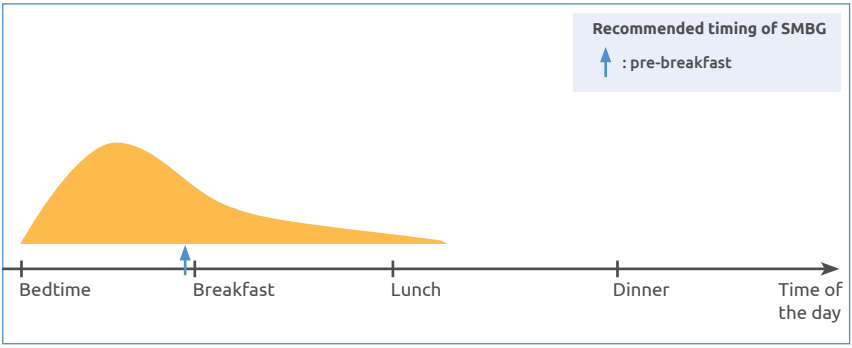
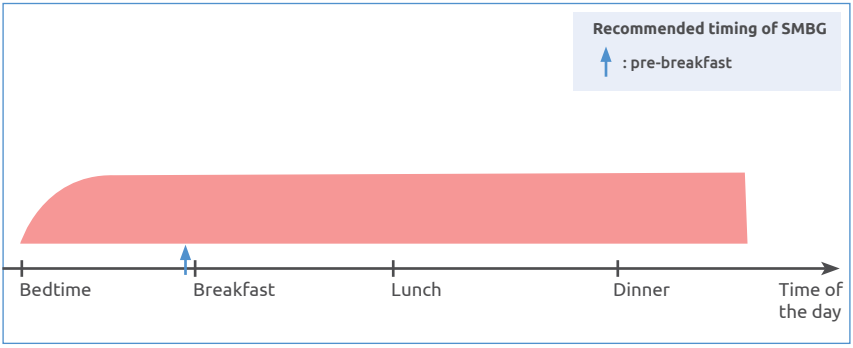
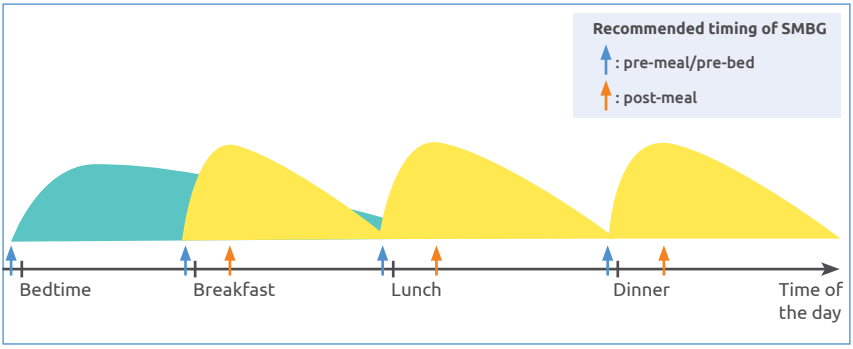


Figure 3-8: OGLDs + once daily basal long acting insulin.



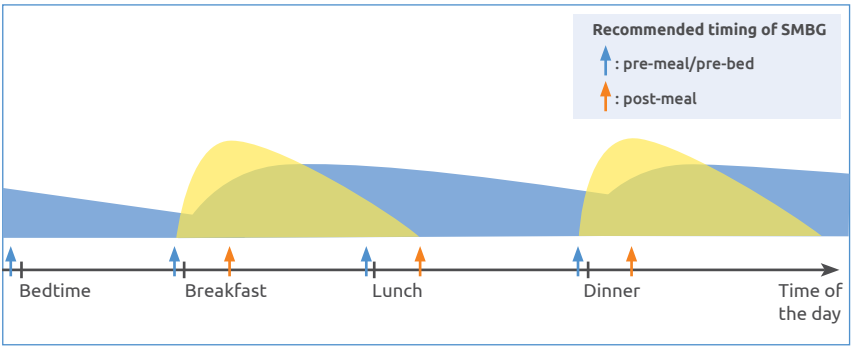
- Readings before breakfast give information about pre-bed intermediate acting insulin (Figure 3-7) or once daily long acting insulin (Figure 3-8).

Figure 3-9: Basal bolus insulin regimen.



- Readings before breakfast give information about pre-dinner or pre-bed intermediate acting insulin.
- Readings before other main meals (pre-lunch or pre-dinner) reflect short acting insulin taken at the previous meal.
- Readings at pre-bed give information about short acting insulin given before dinner (Figure 3-9).

Figure 3-10: Twice daily premixed human insulin regimen.



- Readings before breakfast give information about pre-dinner intermediate.
- Readings at pre-lunch give information about short acting insulin given before breakfast.
- Readings at pre-dinner give information about the intermediate acting insulin given before breakfast.
- Readings at pre-bed give information about short acting insulin given before dinner.
- Monitoring of readings at post-meal is recommended when readings at pre-meal are on target (Figure 3-10).

Figure 3-11: Twice daily premixed insulin analogue.

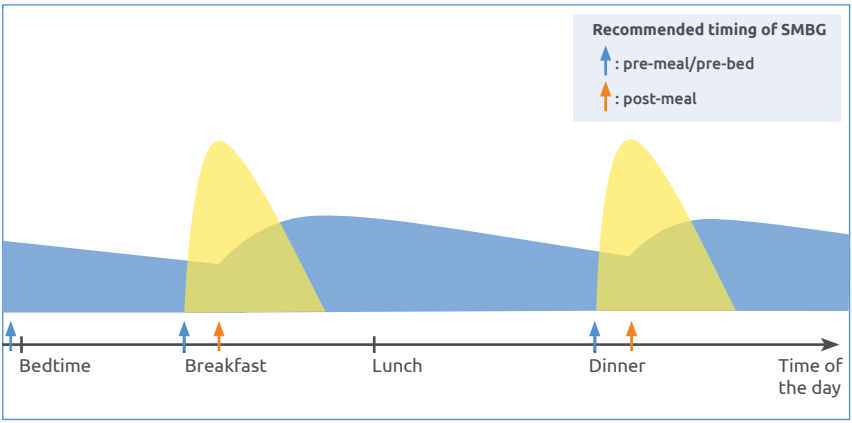
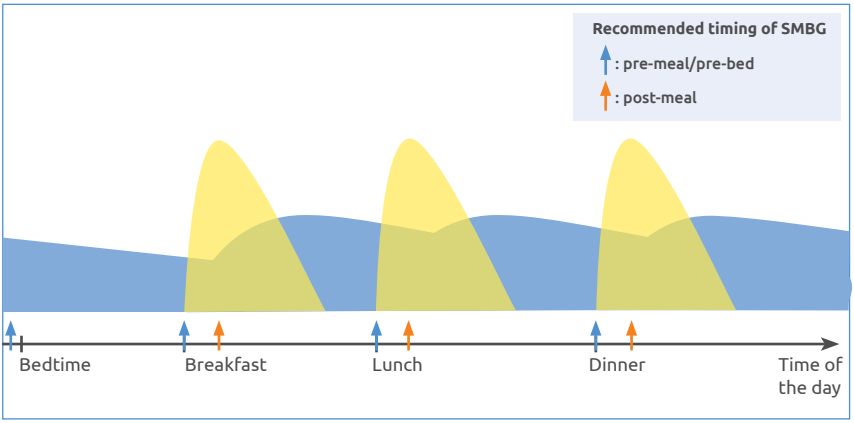


Figure 3-12: Thrice daily premixed insulin analogue.



- Readings before breakfast give information about pre-dinner long acting insulin.
- Readings at pre-dinner give information about the long acting insulin given before breakfast.
- Readings at post-meal give information about rapid acting insulin given before each meal.
- There is less insulin stacking for twice daily premixed insulin analogue compared to twice daily premixed human insulin (Refer to Figures 3-11 and 3-12).

Role of mobile health (mHealth) in SMBG

- mHealth tools play an emerging role in diabetes prevention and management.[324-328 (Level I)]
- Commonly available mHealth tools include:[324,325 (Level I)]
  - › short-messaging service (sms),
  - › apps (e.g. SMBG diary with or without therapy adjustment).
- mHealth may enhance patient engagement and clinical effectiveness.[324,329 (Level I)]
- mHealth tools should be user-friendly and literacy appropriate.[324,329 (Level I)]
- Compared to usual care, meta-analyses reported a modest reduction in HbA_{1c} by 0.44%-0.55%, increased glycaemic goal attainment and improved self-management.[326-328 (Level I)]
- More research on apps accuracy, data security, accessibility, sustainability and long-term health outcomes is required before large-scale implementation.[325 (Level I)]

For monitoring of glycaemic control in specific populations such as during Ramadan fasting (available online at: https://www.diabetesmalaysia.com.my/article.php?aid=224), pregnancy (available online at: http://www.acadmed.org.my/index.cfm?&menuid=67) and inpatients setting (Ministry of Health Malaysia. Practical Guide to Inpatient Glycaemic Care, 2nd edition, May 2020), please refer to the relevant Malaysian guidelines.

3.8.3 Continuous glucose monitoring (CGM)

- CGM measures interstitial glucose (which correlates closely to plasma glucose) via a subcutaneously inserted sensor.
- Glucose readings are measured every 5 to 15 minutes.
- CGM can be classified into two types, retrospective (professional) and real-time (personal or flash).

Table 3-23: Comparison of professional, personal or flash CGM.

Type of CGM	Professional CGM	Personal CGM	Flash CGM
Usage frequency	Intermittent	Intermittent / Continuous	Intermittent / Continuous
Glucose data display	Retrospective / Blinded	Real-time glucose levels with trend arrows and graphic display	On demand real-time glucose levels with trend arrows and graphic display
Capillary plasma glucose calibration	Required	Variable depending on device	Not required*
Hypo-/ Hyperglycaemia alarm	x	√	x
Devices required	Sensor, recorder	Sensor, transmitter, display unit[a]	Sensor, reader / mobile app
Sensor lifespan	6 days	6-90 days	14 days
User training requirement	+	++	+
Integration with insulin pump	x	√[b]	x
Report download	√	√	√
Cost	++	+++	+
Interference / Precaution of use	Paracetamol#		-
	MRI / X-ray, diving (>1 m depth for >30 min)		

[a] Insulin pump, portable diabetes assistant or mobile app (bluetooth link)
[b] Medtronic 640G insulin pump
** factory calibrated; # may cause falsely elevated glucose readings up to 8 hours post ingestion.*[330 (Level II-2)]
CGM: continuous glucose monitoring; MRI; magnetic resonance imaging.

Clinical benefits of CGM in the management of T2DM

- There is emerging evidence that CGM application in people with T2DM provide a number of clinical benefits.
  - › Detection of unrecognised hypoglycaemia/hyperglycaemia and evaluation of glycaemic variability.
    - It provides objective insights into the key glucose metric i.e. time in range (TIR).[331,332 (Level II-1) 333,334 (Level II-2)]

- TIR is defined as percentage of glucose reading and time per day within the target range of 3.9 mmol/L-10.0 mmol/L by the International Consensus on TIR.[335 (Level III)]

› Improved glycaemic control (HbA_{1c}) and/or TIR.
  - Shows improvement of HbA_{1c} ranging between 0.3%-0.7%.[336-341 (Level I) 342 (Level II)]
  - Reduction in hypoglycaemia and increase in TIR.[339,343 (Level I)]
  - Flash CGM users reported higher treatment satisfaction.[340,341,343 (Level I)]

› Effective motivational tool in improving adherence to therapeutic lifestyle modification.[338,344,345 (Level I) 342 (Level II-2)]

Limitations and barriers to CGM use

- Cost/reimbursements – CGM is costly and not routinely reimbursed.
- Technological barriers – it is more important to focus on the overall glycaemic patterns and trends than to focus on the absolute glucose levels. Accuracy tends to be lower:[346-348 (Level II-2) 349,350 (Level III)]
  - › during the first 24 hours of sensor insertion,
  - › in the low end of glycaemic range; and
  - › during the phase of rapidly changing glucose levels related to time-lag between interstitial and plasma glucose.
- Human (user) factors – adequate training is required for proper use and interpretation of the report.[335,349,351 (Level III)]

Considerations for use of CGM in T2DM

- Advances in CGM technology have made it a potentially useful tool in the day-to-day management of T2DM and may be considered in the following situations:
  - › HbA_{1c} above target despite intensive insulin therapy with multiple daily injections [Grade B],
  - › suspected unrecognised hypoglycaemia, impaired hypoglycaemia awareness, dawn phenomenon or delayed postprandial hyperglycaemia [Grade B],
  - › Special populations at high risk of severe hypoglycaemia (e.g. the elderly, patients with advanced DKD) [Grade C], and
  - › Discrepant HbA_{1c} with SMBG [Grade C].
- The choice and frequency of CGM devices should be individualised depending on the primary goal and patients' willingness to be actively engaged in their day-to-day glucose management.
- To derive maximum benefits, it is essential to provide structured diabetes education, training and support, assisted by a diabetes nurse educator.

3.8.4 Monitoring of other risk factors

- Monitoring of glycaemic control, co-morbidities, complications and other CVD risk factors should follow the schedule as laid out in Table 3-24.

Table 3-24: Clinical monitoring schedule for other risk factors in patients with T2DM.

Test	Initial visit	3-monthly OR Every follow-up visit	At annual visit
Physical examination			
Weight	√	√	√
Waist circumference	√	√	√
BMI	√		√
BP	√	√	√
Eye[a]			
Visual acuity	√		√
Fundoscopy/Fundus camera	√		√
Feet			
Pulses/ABI	√	√	√
Neuropathy	√	√	√
Dental check-up	√		√
ECG[b]	√		√
Laboratory investigations			
Plasma glucose	√	√	√
HbA_{1c}	√	√	√
Lipid profile[c]	√		√
Creatinine/BUSE + eGFR[d]	√		√
LFT (AST, ALT)	√		√
Urine microscopy	√		√
Urine albumin/microalbumin/ spot morning urinary ACR	√		√

√: conduct test ■ *conduct test if abnormal on initial visit or symptomatic* ■ *no test is required*

[a] Refer table 5-1 (Section 5.1) – 1-2 yearly if no diabetic retinopathy, more frequently according to retinopathy status.
[b] Baseline resting ECG is recommended. If abnormal, refer to cardiology. However, if resting ECG is normal, further screening for CVD is not recommended in asymptomatic patients with high risk of ASCVD, provided they are receiving intensive medical therapy for optimal CV risk factor control (Refer Section 5.4). To date, CV risk assessment in asymptomatic patients is still controversial and evidence is evolving.
[c] Once statin is initiated, suggest checking lipid profile every 4-to-12 weeks to ascertain efficacy and adherence, and annually thereafter (Refer Section 3.9.2).
[d] Serum creatinine with calculated eGFR, preferably using CKD-EPI formula (Refer Section 5.2).

BMI: body mass index; BP: blood pressure; ABI: ankle brachial index; ECG: electrocardiogram; BUSE: blood urea and serum electrolytes; eGFR: estimated glomerular filtration rate; LFT: liver function test; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ACR: albumin-to-creatinine ratio; CVD: cardiovascular disease; ASCVD: atherosclerotic cardiovascular disease; CV: cardiovascular.

Adapted from Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation (IDF) Western Pacific Region, 2005[352] (Level III) and Standards of Medical Care in Diabetes 2020.[6] (Level III)

Recommendations: Monitoring

1. Glycaemic targets must be individualised. Therapy in most patients with T2DM should be targeted to achieve an HbA_{1c}≤7.0% or 6.5% (where appropriate), if achievable without significant hypoglycaemia. Reduction in HbA_{1c} has been shown to decrease the risk of: a. microvascular complications b. macrovascular complications	 *Grade A* *Grade B*
2. To achieve HbA_{1c} ≤7.0%, aim for FPG or pre-prandial glucose targets of 4.4-7.0 mmol/L and 2-hour PPG target of 4.4-8.5 mmol/L.	*Grade B*
3. SMBG should be recommended in patients on insulin and is desirable for those on OGLDs.	*Grade C*
4. CGM may be considered in patients with suboptimal HbA_{1c} or suspected to have unrecognised hypoglycaemia on intensive insulin therapy.	*Grade B*
5. Monitoring of glycaemic control, co-morbidities, complications and other CVD risk factors should be done at initial visit and whenever indicated subsequently.	*Grade C*

3.9 Management of co-morbidities in T2DM

SUMMARY OF UPDATES

- Hypertension:
  - Target for initiation of treatment is systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg.
  - Treatment target is SBP 130-139 mmHg and DBP 70-79 mmHg.
- Hyperlipidaemia
  - All individuals with T2DM over the age of 40 should be treated with a statin regardless of baseline LDL-cholesterol (LDL-C) level.
  - LDL-C targets have recently been revised to lower levels, according to category of CV risk.
- Obesity
  - A structured lifestyle modification that includes dietary intervention with VLCD (≤800 kcal) using MRP products has been shown to be effective in weight loss and reducing HbA_{1c} in overweight and obese T2DM. Successful weight reduction of >15% of body weight can result in diabetes remission.
  - S/C liraglutide 3.0 mg daily, a recently approved anti-obesity agent, may be effective for weight loss and reducing HbA_{1c}.
  - Comparing lifestyle intervention vs. metabolic surgery, the surgical group achieved better diabetes remission rates and was able to sustain better weight reduction after 2-5 years post-surgery. Metabolic surgery should be considered in those who fulfil the criteria.
- Non-alcoholic fatty liver disease (NAFLD)
  - Metabolic associated fatty liver disease (MAFLD) is a new proposed nomenclature to replace NAFLD as it includes a key driver of this disease which, is presence of metabolic dysfunction.
  - Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among patients with T2DM.
  - T2DM is a risk factor for more severe NAFLD.
  - Lifestyle intervention is the mainstay of treatment for NAFLD.
  - Statin should be prescribed for treatment of dyslipidaemia in NAFLD patients to reduce the risk of CVD.
  - Patients suspected or confirmed to have more severe NAFLD should be considered for referral to Gastroenterologist/Hepatologist for further evaluation and management.

3.9.1 Hypertension and T2DM

- Hypertension is a common co-morbidity of T2DM, with a prevalence of 80.4% among patients who are followed up in the National Diabetes Registry.[3 (Level II-3)]
- Hypertension should be detected and treated early in the course of T2DM to prevent CVD and to delay the progression of renal disease and diabetic retinopathy.
- Reduction in systolic blood pressure (SBP) of 10 mmHg or diastolic blood pressure (DBP) of 5 mmHg, irrespective of whether the patient has T2DM, is associated with significant reductions in all major CV events by 20%, all-cause mortality by 15%, stroke by 35%, coronary events by 20% and heart failure by 40%.[353,354 (Level I)]

Treatment threshold

- Pharmacological treatment should be initiated in patients with T2DM when BP is persistently ≥140 mmHg systolic and/or ≥ 90 mmHg diastolic.
  - › Meta-analyses have consistently shown significant risk reduction in mortality, CHD, cerebrovascular disease and heart failure when treatment is started at SBP ≥140 mm Hg. [355,356 (Level I)] and DBP >90 mmHg.[354 (Level I)]
- Two meta-analyses[354,355 (Level I)] showed that lowering BP when initial SBP is <140 mmHg, showed no additional CV benefits. Moreover, a more recent systematic review found that it increased the risk of CV death (HR 1.15, 95% CI 1.00,1.32), with no observed extra benefit in MI, stroke, heart failure or ESKD.[356 (Level I)]
- There is insufficient evidence to date for benefits of starting treatment when DBP is <90 mmHg (e.g. patients with high normal BP or 130-139/85-89 mmHg).[357 (Level I)]

Treatment target for SBP and DBP

- The ACCORD trial[358 (Level I)] showed no benefit in combined CV endpoints with SBP <120 mmHg vs. <140 mmHg.
- A more recent meta-analysis[359 (Level I)] demonstrated an increase of adverse events,[357 (Level I)] with SBP <130 mmHg.
- In contrast, the SPRINT trial (patients with hypertension without T2DM), lowering SBP to <120 mmHg vs. <140 mmHg resulted in 25% lower rates of primary composite outcomes of MI, other acute coronary syndromes, stroke, heart failure or death from CV causes.[360 (Level I)]
- In high risk patients with T2DM and coronary artery disease, lowering SBP to <120 mmHg and DBP <70 mmHg, studies[361-366 (Level I)] report adverse CV outcomes supporting the existence of a J-curve phenomenon. This supports targets for SBP of 130-139 mmHg and DBP 70-79 mmHg.[(Level I)]

- In those who do not have pre-existing CHD, but have a higher risk of stroke (such as Asian patients) and DKD, lower SBP target of <130 mmHg (but not <120 mmHg) might be appropriate provided that it is well tolerated, to lower the risk of stroke[359 (Level I)] and albuminuria.[355,367 (Level I)]

Management

- Non-pharmacological management cannot be overemphasized.
  - › Dietary counselling should target an optimal body weight.
  - › Dietary sodium restriction is advisable.
- Renin-angiotensin system (RAS) blockers are the first-line pharmacological treatment of choice for patients with T2DM and hypertension.
  - › They are found to be more effective than other drug classes in reducing the risk of CHD, all-cause death and composite of stroke, CHD, and heart failure.[359 (Level I)]
- ACE inhibitors have been regarded as drug of choice based on extensive data.[368,369 (Level I)]
  - › If an ACE inhibitor is not tolerated, an ARB should be considered.[370 (Level I)]
  - › ARBs have been reported to be superior to other non-RAS blocker antihypertensive drugs in terms of slowing the progression of nephropathy at the microalbuminuric and overt nephropathy stages.[370-373 (Level I)]
- Multiple drug therapy is generally required to achieve BP targets.
  - › 90% of patients require three antihypertensive medications to achieve target.[117 (Level I)]
  - › Diuretics, calcium channel blockers (CCBs), beta-blockers and peripheral alpha-blockers may be used as add-on therapy.
- Combination ACE inhibitor and ARB is not recommended.[374 (Level I)]

Table 3-25: Anti-hypertensive drugs for T2DM.

	Diuretics	β-blockers	ACE inhibitors	CCB	Peripheral α-blockers	ARB
T2DM without nephropathy	+	+/-	+++	+	+/-	++
T2DM with nephropathy	++	+/-	+++	++	+/-	+++

The grading of recommendation from (+) to (+++) is based on increasing levels of evidence and/or current widely accepted practice. (+/-) indicates to use with care.
ACE: angiotensin-converting enzyme; CCB: calcium channel blocker; ARB: angiotensin-receptor blocker.

Adapted from Malaysian CPG for Management of Hypertension (5th ed) 2018.[375 (Level III)]

Recommendations: Hypertension and T2DM

1. For patients with T2DM, the treatment threshold for starting pharmacological therapy is ≥140 mmHg systolic and/or ≥90 mmHg diastolic.	*Grade A*
2. No CV benefit is seen for starting pharmacological therapy in patients with T2DM whose BP are in the high normal range: 130-139/80-89 mmHg.	*Grade A*
3. In patients with T2DM with hypertension, it is recommended for individuals without pre-existing CHD and who are at higher risk of stroke or DKD to:	
a. target SBP <130 mmHg (if tolerated but, not to <120 mmHg),	*Grade A*
b. target DBP to 70-79 mmHg, but not <70 mmHg.	*Grade A*
4. Pharmacological treatment should be initiated in patients with T2DM when the BP is persistently ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic.	*Grade A*
5. ARBs or ACEIs are the first-line BP agents of choice for patients with T2DM and hypertension.	*Grade A*
6. Combined use of ACE-i and ARB is not recommended.	*Grade A*

3.9.2 Hyperlipidaemia and T2DM

- T2DM is a CHD defining disease.
- Control of hyperglycaemia alone has a modest and heterogeneous effect on reduction of CVD.[310,376 (Level I)] and may take long periods to manifest.[377 (Level I)]
- In contrast, multifactorial intervention has been shown to reduce microvascular complications, CV events and mortality in the STENO-2 study.[35,36 (Level I)]
- Thus, efforts must also be directed to address other risk factors such as dyslipidaemia, hypertension and prior CV events.

Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals.
  - › Non-fasting sample can be used for assessment of lipid parameters.
  - › If non-fasting TG is elevated (>2.3 mmol/L), a fasting sample is required.
- In adolescents with T2DM, screening for lipid disorders should be done at diagnosis after glycaemic control is achieved. If lipid values are within targets, screening should be repeated annually thereafter.[6,378-380 (Level III)]
- CV risk calculators for primary prevention are not recommended as individuals with T2DM are already considered high risk and all CV risk factors should be aggressively managed (Refer to Section 5.4-A).

Targets

A. Primary target: LDL-C

- All patients over the age of 40 should be treated with a statin regardless of baseline LDL cholesterol level (Refer Table 3-26).[381,382 (Level I)]
  - › Statin is not recommended in women of child-bearing potential who are not using adequate contraception and is contraindicated during pregnancy.
- The LDL-C targets depends on the patient's CV risk category (Table 3-26).
  - › Very low LDL-C level achieved by newer lipid lowering drugs had shown further CV risk reduction in large scale clinical trials proportionate to the degree of LDL-C lowering.[383-390 (Level I)] The absolute risk reduction is most evident in patients with higher CV risk.

Table 3-26: LDL-C targets.

Risk categories for patients with T2DM		Target LDL-C (mmol/L)	Target Non-HDL-C (mmol/L)
Very high risk[383-386] (Level I)	Patients with diabetes and established CVD **OR** Other target organ damage **OR** ≥3 risk factors	<1.4	<2.2
High risk[383,386 (Level I)]	Patients with diabetes for ≥10 years without target organ damage **AND** any other additional risk factor	<1.8	<2.6

Moderate risk[383,386] (Level I)	<50-year-old with T2DM of <10 years duration without other risk factors	<2.6	<3.4

Non-HDL-C: calculated as Total cholesterol – HDL-C. LDL-C targets depends on the patients' CV risks as detailed above.
LDL-C: low-density lipoprotein cholesterol; Non-HDL-C: Non-high-density lipoprotein cholesterol; CVD: cardiovascular disease.

Adapted from Cosentino F, et al. 2020.[43]

- If the above targets are unattainable, aim for a 50% reduction of pre-treatment LDL-C level.[383,386] (Level I)

B. Secondary targets: Non-HDL-C, HDL-C and TG

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

Table 3-27: Secondary targets.

Parameter	Targets
Non-HDL-C	0.8 mmol/L above the LDL-C target according to risk category (Refer Table 3-30)
HDL-C	>1.0 mmol/L for males; >1.3 mmol/L for females
TG	< 1.7 mmol/L

Non-HDL-C: Non-high-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol.

Adapted from Mach F, et al. 2020.[391]

Management

- Lifestyle modification focusing on:
  - reduction of saturated fat, trans-fat and cholesterol intake,
  - increasing intake of dietary n-3 fatty acids, viscous fibre and plant stanols / sterols,
  - weight loss (if indicated); and
  - increasing physical activity
- Lowering LDL-C is the main aim of treatment and statins are the first-line lipid lowering drug.
- Statin therapy should be intensified to achieve LDL-C goal before considering combination therapy.
- If the target LDL-C is not achieved with maximal tolerated dose of statin therapy, combination therapy with ezetimibe is recommended.[384,385] (Level I)

- For very high-risk patients, Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors should be considered if maximal tolerated dose of statin and ezetimibe fail to achieve LDL-C targets.[387-390 (Level I)]
- In patients with high TG, improving diabetes control and lifestyle modification is emphasized.
- Investigate for secondary causes, if fasting TG >5.7 mmol/L and consider pharmacological therapy with fibrate and/or fish oil (2-4g/day) to reduce the risk of pancreatitis.
- Nicotinic acid should only be used in patients with high risk of pancreatitis with a TG level of >10 mmol/L, in those who do not respond adequately to fibrates and/or fish oil.[392-394 (Level I)]
- In patients with ASCVD or high CV risk and elevated triglycerides, the addition of icosapent ethyl 4 mg/day to statin has been shown to reduce CV risk by 25%.[395 (Level I)]
- In patients with TG >2.3 mmol/L and low HDL-C, fibrates may be considered in combination with statin.[396-399 (Level III)]
- In patients with established retinopathy, fenofibrate reduces progression of diabetic retinopathy, irrespective of baseline TG/HDL-C level.[400,401 (Level I)]
- In T2DM patients below 21-year-old without clinical ASCVD, statin is generally not recommended.[378-380 (Level III)]

Table 3-28: Lipid lowering drugs for dyslipidaemia in T2DM.

Lipid goal	Initial drug	Suggested addition in order of preference
Lower LDL-C	Statins	Ezetimibe PCSK9 inhibitor BAS (may increase TG)
Lower TG	Fibrates	Omega-3 fatty acid Statins* Nicotinic acid**
Treat combined hyperlipidaemia	Statins*	Fibrates BAS and fibrates PCSK9 Ezetimibe

**High dose may be required; **With careful monitoring and keeping dose <1.5 g/day.*
LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; BAS: bile acid sequestrants.

Table 3-29: Effect of lipid lowering therapy on lipids.*

Lipid lowering therapy	LDL-C	TG	HDL-C
Statin	↓ 30%-60%	↓ 10%-20%	↑ 1%-10%
BAS	↓ 20%-30%	May ↑	↔
Ezetimibe	↓ 10%-20%	↓ 10%	↑ 1%-5%
PCSK9 inhibitor	↓ 60%	↓ 25%	↑ 10%
Fibrate	↓20%	↓ 25%-50%	↑ 10%-20%
Omega 3 fatty acid (2-4g)	Variable effect	↓ 20%-45%	↑ 1%-10%
Nicotinic acid	↓10%-20%	↓ 20%-50%	↑ 20%-25%

**Effect varies with individual, baseline lipid levels and, dose and type of drugs used.*
LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; BAS: bile acid sequestrants. Data extracted from Mach F, et al. 2020.[391]

Table 3-30: Effect of various statins on LDL-C.

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering	≥ 50%	30-49%	<30%
Statins	Atorvastatin 40-80 mg	Atorvastatin 10-20mg	
	Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	
		Simvastatin 20-40 mg	Simvastatin 10 mg
		Pravastatin 40-80mg Lovastatin 40-80 mg	Pravastatin 10-20 mg Lovastatin 20 mg

LDL-C: low-density lipoprotein cholesterol.

Adapted from Stone NH, et al.2014.[402]

Recommendations: Dyslipidaemia and T2DM

1. All patients over the age of 40 should be treated with a statin regardless of baseline LDL-cholesterol levels.	*Grade A*
2. Statin therapy should be intensified to achieve LDL-C goal based on CV risk.	*Grade A*

3.9.3 Obesity and T2DM

- In the Malaysian National Health Morbidity Survey (NHMS) 2015, 33.4% and 30.6% of adults (>18 years old) were overweight and obese (BMI according to the Malaysian CPG on Management of Obesity, 2004).[403,404]
- Based on the 2019 National Diabetes Registry[405] (Level II-3) data sourced from primary care health clinics, 84% of individuals with T2DM are either overweight or obese (Available at: *http://ndr.moh.gov.my/report/clinical_audit/crn1*). People with diabetes who are overweight or obese have higher risk of complications.
- Lifestyle intervention focusing on weight loss showed improvement in HbA_{1c} and other CV risk factors.[79,406] (Level I)
- Many GLDs 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 3-31 shows the GLDs and their effect on weight.

Table 3-31: GLDs and their effect on weight.

Weight gain	Weight neutral	Weight loss
Insulin	Metformin	GLP1-RA
TZDs	AGIs	SGLT2-i
SU	DPP4-i	
Meglitinides		

TZDs: thiazolidinediones; SU: sulphonylurea; AGIs: alpha-glucosidase inhibitors; DPP4-i: dipeptidyl peptidase-4 inhibitors; GLP1-RA: glucagon-like peptide 1 receptor agonists; SGLT2-1: sodium-glucose cotransporter 2 inhibitors.

Adapted from Lau DC et al. Can J Diabetes 2015.[407]

Assessment and treatment of overweight and obesity

- The initial assessment of people with diabetes should include height, weight, BMI (kg/m^2) and waist circumference.
- Weight loss of between 5%-10% will improve glycaemic control, BP, lipid profile and QoL.[79,406] (Level I)
- The goals of therapy are to achieve optimal glycaemic and metabolic control.
- The mainstay of treatment should be through lifestyle modification which include behavioural change, physical activity and dietary interventions (Refer Sections 3.5.1 & 3.5.2).

Table 3-32: Classification of weight by BMI.

Classification	BMI (kg/m^2)	Risk of co-morbidities
Underweight	<18.5	Low (but increased risk of other clinical problems
Normal range	18.5-22.9	Optimal
Overweight	≥23.0	
• Pre-obese	23.0-27.4	Increased
• Obese I	27.5-34.9	High
• Obese II	35.0-39.9	Very High
• Obese III	≥40.0	Extremely high

Classification of BMI based on the Malaysian CPG on Management of Obesity, 2004.[403]

Adapted from WHO Consultation Group.[404] *BMI: body mass index.*

Management

A. Non-pharmacological intervention

- Nutritionally balanced, energy-reduced dietary interventions are recommended for healthier body weight to be achieved (Refer Section 3.5.1).
  - › Weight loss >5% is needed to see beneficial effect on HbA_{1c}, lipid and BP.[79,408 (Level I)]
  - › Caloric restriction of 1200-1500 kcal/day for women and 1500-1800 kcal/day for men is useful for rapid weight loss.[77 (Level I)]
- Use of MRP, with close patient monitoring, can be beneficial. DiRECT, an open randomised trial involving overweight or obese patients with T2DM were treated with total diet replacement (825 kcal) at primary care level. A significant weight loss of 15 kg (24%) and diabetes remission (46%) were seen in the intervention group.[95 (Level I)]
- Very low calorie diet (VLCD) with a total MRP of <800 kcal/day may achieve greater short-term weight loss (10%-15%) with greater glycaemic improvement, as shown in the DROPLET study.[409 (Level I)]
  - › Overweight or obese subjects were managed by their primary care doctors and given MRP for 8 weeks followed by food re-introduction over 4 weeks.
  - › At week 13 onwards, subjects were encouraged to take MRP once or twice daily.
  - › Significant weight loss at week 12, -9.6 kg (-11.0 kg to -8.2 kg) was seen and was sustained at 12 months, -7.2 kg (-9.4 kg to -4.9 kg).
  - › Risk of weight rebound after discontinuing the program was not seen in this study.

- Increased physical activity consisting of at least 150 minute/week of moderate-intensity exercise (Refer Section 3.5.2).
  - This includes muscle strengthening and resistance exercise 2 to 3 times/ week. [410 (Level III)]
  - Overweight or obese persons with T2DM should increase the exercise duration to >60 minutes per day/approximately 450 minutes per/week for weight reduction.[135 (Level III)]
- Frequent contact with healthcare providers and behavioural therapy should be part of the intervention.

B. Pharmacological intervention

- Pharmacotherapy can be considered for patients with T2DM with BMI ≥27.0 kg/m^2 after failing 6 months of lifestyle modification.[403 (Level III)]
- Three anti-obesity agents have been approved, phentermine,[411,412 (Level I) 413 (Level II-1)] orlistat[414-416 (Level I) 417 (Level II-3)] and high dose liraglutide (3 mg/day)[408,418-422 (Level I)] for the management of obesity.

Table 3-33: Approved anti-obesity drugs.

Drug	Class	MOA	Recommended duration	Net weight loss (kg)	Precautions and side effects
Phentermine[411, 412 (Level I) 413 (Level II-1)]	Sympatho-mimetic amine	Appetite suppression	3 months (can be used cyclically)	3.6	• Only indicated for short-term use. • Precautions in poorly controlled BP and coronary artery disease
Orlistat[414-416 (Level I) 417 (Level II-3)]	Lipase inhibitor	Reduces GI fat absorption	Up to 4 years	6.9	• Liquid or oily stool, oil leakage from rectum and flatulence. • MVT replacements if used >12 months.

Liraglutide, 3.0 mg[408,418-422] (Level I)	GLP-1 RA	Slows gastric motility, reduces satiety	56 weeks	6.4	• Nausea and vomiting • Pancreatitis • Cholelithiasis

BP: blood pressure; GI: gastrointestinal; GLP1-RA: glucagon-like peptide 1 receptor agonists; MVT: multivitamins.

C. Surgical intervention

- Bariatric surgery should be considered when lifestyle and pharmacological interventions have failed in the obese with T2DM and at high CVD risk with suboptimal glycaemic control.[403] (Level III)
- International diabetes organisations developed a consensus treatment[423] (Level III) algorithm for metabolic surgery in T2DM (Diabetes Surgery Summit-II, DSS-II). Metabolic surgery should be recommended for Asians with T2DM as below:
  - › ≥37.5 kg/m^2,
  - › ≥32.5 kg/m^2 to 37.4 kg/m^2 with inadequately controlled hyperglycaemia despite lifestyle modification and optimal medical treatment; and
  - › ≥27.5 kg/m^2 to 32.5 kg/m^2 - it can be considered in those with inadequately controlled hyperglycaemia despite optimal medical treatment.
- The Asian Consensus Meeting on Metabolic Surgery (ACMOMS) recommends bariatric surgery for the following persons with diabetes:*[424] (Level III)
  - › >32 kg/m^2
  - › >30 kg/m^2 with 1 or more features of metabolic syndrome

  *After review of the ACMOMS and DSS-II consensus, the evidence supports the efficacy of bariatric surgery in the above individuals. However, this should be performed at centres of excellence that perform high-volume surgery.
- Evaluation for the appropriateness of surgery should be performed by a multidisciplinary team consisting of endocrinologist, bariatric surgeon, psychiatrist, dietitian and physiotherapist prior to surgery.[423] (Level III)

Table 3-34: Criteria for bariatric surgery.

Factors	Criteria
Weight loss history	Failure of previous attempts at weight reduction, including programs such as weight watchers etc.
Commitment	Expectation that patient will adhere to postoperative care consisting of: • follow up visits with health care team, • adherence to medical management, • continued dietary restriction
Exclusion criteria	• BMI <30 kg/m^2 or <27.5 kg/m^2 for Asians • Current drug or alcohol abuse • Severe psychiatric illness • Lack of comprehension of the benefits, risks, expected outcomes and required lifestyle changes

BMI: body mass index.

Adapted from Mechanick JI, et al. Obesity 2009.[425]

- Choice of procedure
  - › Bariatric surgery procedures can be classified as restrictive or malabsorptive or combined restrictive and malabsorptive.[424,426-428 (Level I)]
    - The most commonly performed surgical procedures for reversing/improving diabetes are roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG).[427,429 (Level I)]
    - Laparoscopic adjustable gastric banding (LAGB) has been demonstrated to have intermediate success.[427,429 (Level I)]
- Recent meta-analyses reports show mean excess weight loss 10 years after bariatric surgery is 56.7%, 74.1%, 58.3%, 45.9% in RYGB, Biliopancreatic diversion (BPD), SG and LAGB respectively.[429,430 (Level I)]
- The magnitude of HbA_{1c} reduction ranges between 2.5%-2.8% for SG[431,432] and 2.6%-4.4% for RYBG.[433-435 (Level I)]

- In addition, there is metabolic improvement as shown in Table 3-35 below.

Table 3-35: Metabolic improvement associated with bariatric surgery.

Disease	% of Improvement or remission		
	At 2 years	At 5-7 years	At 10 years
T2DM	72%[436] 80.3%[426]	54%[437] 88%[432]	36%[436]
Hypertension	24%[436]	66%[438]	41%[436]
Hypertriglyceridaemia	62%[436]	82%[439]	46%[436]
Hypercholesterolaemia	22%[436]	53%[440]	21%[436]
NAFLD	84% steatosis resolution, 75% fibrosis resolution[441]		

NAFLD: non-alcoholic fatty liver disease.

Adapted from Vest AR et al. Circulation; 2013.[442]

- The ABCD (age, BMI, c-peptide, duration) score is a surgical scoring for T2DM patients to predict the success of surgical intervention (Refer Table 3-36). With a score of ≥4, the remission rate for T2DM is >50%.[443] (Level II-2)

Table 3-36: ABCD score for prediction of T2DM remission

Variable	Points on ABCD index for gastric bypass			
	0	1	2	3
Age	≥40	<40		
BMI (kg/m^2)	<27	27-34.9	35-41.9	≥42
c-peptide (mmol/L)	<2	2-2.9	3-4.9	≥5
Duration of T2DM (years)	>8	4-8	1-3.9	<1

The age, BMI, c-peptide and duration of T2DM (ABCD) scoring. The total possible score value range from 0-10. The higher the score, the higher percentage for T2DM remission.

Adapted from Lee WJ et al. Surg Obes Relat Dis; 2013.[443] (Level II-2)

Recommendations: Obesity and T2DM

1. In overweight or obese persons with diabetes, at each clinic encounter, BMI and waist circumference should be measured and documented.	*Grade A*
2. Overweight or obese persons with T2DM should be strongly advised to aim for a target weight loss of 5%-10% and be informed of the health benefits.	*Grade A*
3. A structured program of lifestyle modification that includes low calorie diet and regular physical activity (250-450 minutes/week) has been shown to improve glycaemic control and weight loss.	*Grade A*
4. MRP and VLCD dietary intervention can be considered in selected patients with aims of achieving diabetes remission.	*Grade B*
5. The use of anti-obesity agents in obese T2DM patients is an effective option for those who fail lifestyle intervention.	*Grade A*
6. Bariatric surgery may be considered in those who fulfil the criteria.	*Grade A*

3.9.4 Non-alcoholic fatty liver disease (NAFLD)

- A new proposed nomenclature for NAFLD is "metabolic associated fatty liver disease" or MAFLD. The major benefit of this new nomenclature is a shift towards a diagnosis of inclusion based on the presence of metabolic dysfunction, the key driver of the disease.[949] Note that the following section still refers to NAFLD.
- Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver conditions characterised by excess accumulation of fat in the liver that is associated with chronic overnutrition.[444 (Level II-2)]
- NAFLD is closely associated with obesity and is considered as the liver manifestation of the metabolic syndrome.[444 (Level II-2)]
- For a strict definition of NAFLD, significant alcohol intake (more than two standard drinks/day for men or more one standard drink/day for women), drugs that can cause hepatic steatosis and other causes of liver diseases (e.g. chronic hepatitis B and C virus infection) should be excluded.[444 (Level II-2)]
- Non-alcoholic steatohepatitis (NASH) is the more severe form of NAFLD that is defined histologically by the presence of lobular inflammation and hepatocyte ballooning.[444 (Level II-2)]
- Patients with NASH are more likely to develop liver fibrosis and cirrhosis, and hepatocellular carcinoma (HCC).[444 (Level II-2)]
- T2DM is a risk factor for NASH and advanced liver fibrosis,[445 (Level II-2)] which is one of the leading causes of liver transplantation for cirrhosis and for HCC.[446,447 (Level II-2)]
- In Malaysia, the prevalence of NAFLD among patients with T2DM has been estimated to be 49.6% based on ultrasonography and 72.4% based on controlled attenuation parameter.[448 (Level II-2)]
- A study using liver stiffness measurement (measured using transient elastography e.g. Fibroscan; a non-invasive procedure) estimated the prevalence of advanced liver fibrosis among patients with diabetes mellitus to be 21.0%.[449 (Level II-2)]
- The same study using liver stiffness measurement ≥8 kPa to identify patients with diabetes mellitus for liver biopsy found that the majority of the patients had NASH (83.1%) and some degree of liver fibrosis (87.1%), while advanced liver fibrosis was diagnosed in 36.6%.[449 (Level II-2)]

Assessment

Table 3-37: Modalities for NAFLD assessment and recommended intervals for testing.

Assessment	Result	Action	
Blood tests (e.g. ALT and AST)	Normal ALT and AST	Repeat ALT and AST annually	
	Elevated ALT and AST*	• US abdomen to diagnose fatty liver/exclude focal liver lesion • Repeat ALT and AST after 3-6 months	• Exclude other causes of liver disease • Consider referral to Gastroenterologist/ Hepatologist
Fibrosis-4 scoring	Fibrosis-4 index <1.3	Repeat every 2-3 years	
	Fibrosis-4 index ≥1.3	Refer for liver stiffness measurement (Refer to Table 3-38)	Consider referral to Gastroenterologist/ Hepatologist

** Exclude possibility of drug-induced liver injury.*
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; US: ultrasound. For Fibrosis-4 index and assessment of NAFLD in T2DM illustrated as a flow chart refer to Appendix 9.

- Drug-induced liver injury is a common cause of elevated ALT and AST.
  - › A careful history about intake of medicines (prescribed, over-the-counter or traditional) or supplements should be obtained.
  - › If the medicine or supplement is considered to be the cause of the elevated AST and ALT, it should be stopped.
  - › The AST and ALT should be repeated 1-3 months later.
- Persistently elevated serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels in patients with T2DM and NAFLD may indicate the presence of NASH. However, normal serum ALT and AST levels do not exclude NASH and advanced liver fibrosis.[450,451 (Level II-2)]
- US examination of the liver should be performed in patients with T2DM and elevated serum ALT and/or AST to diagnose fatty liver and to exclude focal liver lesion.

- Non-invasive fibrosis score, such as fibrosis-4 index (refer to Appendix 9), may be used to risk stratify patients with T2DM and NAFLD.[452,453 (Level II-2)]
  - › Patients with a low score are unlikely to have advanced liver fibrosis, while those with indeterminate or high scores should be referred for liver stiffness measurement.

Table 3-38: Interpretation of liver stiffness measurements and recommended action.

Liver stiffness measurement (kPa)*	Interpretation	Action
<10	Unlikely to have advanced liver fibrosis	
10-15	May have advanced liver fibrosis	• Requires monitoring e.g. repeat in 1 year • Consider referring to Gastroenterologist/ Hepatologist
>15	Likely to have advanced liver fibrosis	• Should be considered for HCC surveillance • Consider referring to Gastroenterologist/ Hepatologist
>20-25 (and/ or presence of thrombocytopaenia)	Likely to have clinically significant portal hypertension	• Should be considered for HCC surveillance and variceal screening • Requires referral to Gastroenterologist/ Hepatologist

**values obtained by transient elastography.*
kPa: kilopascals; HCC: hepatocellular carcinoma.

Adapted from Wong VW, et. Al. 2019.[454 (Level II-2)]

Recommendations: Assessment of NAFLD

1. Patients with T2DM should have platelet count, and serum ALT and AST levels performed for assessment for NASH and advanced liver fibrosis. This may be repeated annually or more frequently, as indicated.	*Grade A*
2. US examination of the liver should be performed in patients with T2DM and elevated serum ALT and/or AST to diagnose fatty liver and to exclude focal liver lesion.	*Grade A*
3. Patients with persistently elevated serum ALT and/or AST level should be investigated to exclude other causes of chronic liver disease.	*Grade A*
4. Patients with indeterminate or high serum biomarkers of fibrosis should be referred for liver stiffness measurement.	*Grade A*
5. Patients with persistently elevated serum ALT and/or AST level or elevated liver stiffness measurement should be considered for referral to Gastroenterologist/Hepatologist for further evaluation and management.	*Grade A*
6. A liver biopsy may be considered for definitive diagnosis of NASH and/or advanced liver fibrosis.	*Grade A*

Treatment

- The mainstay of treatment of NAFLD is lifestyle intervention.[455 (Level II-2)]
  - › A balanced, reduced calorie, individually tailored diet (for overweight/obese persons with T2DM) to enable weight loss which includes limiting excess fructose consumption such as avoiding beverages with added fructose and foods with high fructose corn syrup, choosing complex CHO, high fibre foods and avoiding processed foods.[456 (Level II-2)]
    - A study on biopsy-proven NASH patients found that weight loss of ≥10% through lifestyle intervention over 52 weeks resulted in NASH resolution and fibrosis improvement in 90% and 45% of patients, respectively.[455 (Level II-2)]
  - › Avoid excessive alcohol consumption (refer above).[457 (Level II-2)]
  - › Moderate-intensity exercise ≥30 minutes/day for ≥5 days/week or a total of ≥150 minutes/week, or vigorous-intensity exercise for ≥20 minutes/day for ≥3 days/week or a total of ≥75 minutes/week (any new activity should be started slowly and, its intensity and duration gradually increased).[458 (Level I)]
  - › Smoking cessation to reduce CVD risk.[459 (Level II-1)]
- GLP1-RA has been shown to be associated with significantly greater NASH resolution and lesser fibrosis progression in a randomised, double-blind, placebo-controlled trial.[460 (Level I)]
- SGLT2-i has been shown to significantly reduce liver fat based on magnetic resonance imaging (MRI)-proton density fat fraction (a MRI-based technique for measurement of liver fat) and serum ALT level in a RCT,[461 (Level I)] and may be useful for the treatment of NASH based on a pilot study using paired liver biopsy.[462 (Level II-2)]
- Pioglitazone has been shown to significantly reduce steatosis, lobular inflammation and hepatocyte ballooning in biopsy-proven NASH patients,[463 (Level I)] but its use has been associated with significant weight gain that persisted after discontinuation of therapy. There are also continued concerns about risk of CCF, osteoporosis and bladder cancer.
- Vitamin E has been shown to significantly reduce steatosis, lobular inflammation and hepatocyte ballooning in biopsy-proven NASH patients without T2DM,[463 (Level I)] but its use has been associated with concerns about risk of prostate cancer and increased all-cause mortality.
  - › In a study of biopsy-proven NASH patients with T2DM, vitamin E did not achieve the primary endpoint of 2-point reduction in the NAFLD activity score from 2 different parameters, but did result in significantly greater NASH resolution compared with placebo.[464 (Level I)]

- CVD is the leading cause of mortality in patients with NAFLD. NAFLD and CVD share common risk factors.[465] (Level II-3) Meta-analyses[466,467] (Level II-3) performed demonstrate an association between NAFLD and increased CVD events, especially for those with severe NAFLD or NASH.
  - Risk factors for CVD should be evaluated and managed accordingly to reduce the risk of CVD.
  - Statins reduce the risk of CVD in patients with dyslipidaemia but is under prescribed among patients with NAFLD.
    - In a study on 428 NAFLD patients, 74.1% of patients who should have been receiving statin therapy were not while 58.9% of patients who were on statins did not achieve the treatment LDL-C target.[468] (Level II-2)
    - Serious liver injury from statins is rare and it is safe to be prescribed for most NAFLD patients.

Recommendations: Treatment of NAFLD

1. Lifestyle intervention is the mainstay of treatment of NAFLD.	*Grade A*
2. Statins should be prescribed for treatment of dyslipidaemia in NAFLD patients, when indicated, to reduce the risk of CVD.	*Grade A*
3. GLP1-RA and/or SGLT2-i should be considered for the treatment of T2DM in patients with suspected or confirmed NASH and/or advanced liver fibrosis.	*Grade B*

SECTION 4

MANAGEMENT OF DIABETIC METABOLIC EMERGENCIES

SUMMARY OF UPDATES

- Diabetic ketoacidosis
  - Weight-based fixed rate intravenous insulin infusion (FRIII) is the current standard recommendation and the use of 'sliding scale' insulin should no longer be practised.
- Euglycaemic ketoacidosis
  - Although this has been known in T1DM, it can occur in patients with T2DM treated with SGLT2-i, precipitated by stress, and/or omission of insulin.
  - Awareness, prompt recognition, timely diagnosis and management is required.

4.1 Hypoglycaemia

- Hypoglycaemia is defined by either one of the following three conditions:
  - low plasma glucose level (<3.9 mmol/L);
  - presence of autonomic or neuroglycopenic symptoms (Refer Table 4-1),
  - reversed by CHO intake.

Table 4-1: Symptoms of hypoglycaemia*.

Autonomic	Neuroglycopenic
• Trembling • Palpitations • Sweating • Anxiety • Hunger • Nausea • Tingling	• Difficulty concentrating • Confusion • Weakness/stroke like symptoms • Drowsiness • Vision changes • Difficulty speaking • Headache • Seizures/coma

** Glucose level at which an individual becomes symptomatic is highly variable.*

Table 4-2: Classification of hypoglycaemia.

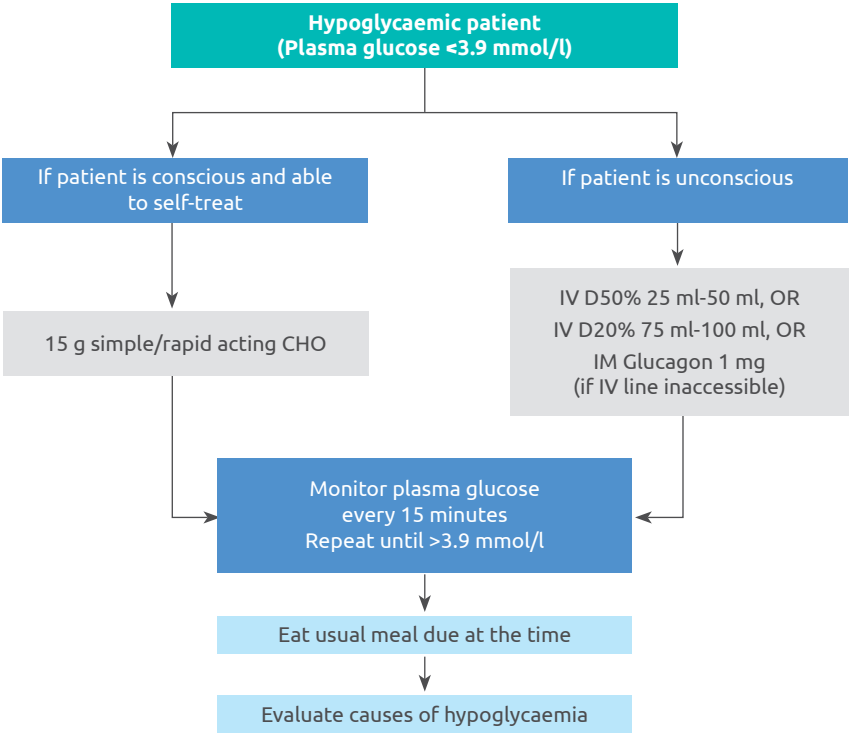
Level	Glycaemic criteria	Description
1	<3.9 mmol/L but ≥3.0 mmol/L	• Recognised as a threshold for neuroendocrine responses to falling glucose in people without diabetes.
2	<3.0 mmol/L	• Threshold at which neuroglycopenic symptoms begin to occur. • Requires immediate action to resolve the hypoglycaemic event.
3	-	• A severe event characterised by altered mental and/or physical functioning that requires assistance from another person for recovery.

- Risk factors for hypoglycaemia include:
  - advancing age,
  - severe cognitive impairment,
  - poor health knowledge,
  - uncontrolled T2DM with glucose variability,
  - hypoglycaemia unawareness,
  - long duration of insulin therapy,
  - renal and hepatic impairment,
  - peripheral and autonomic neuropathy.
- Strategies for prevention of hypoglycaemia:
  - identifying patients at risk,
  - education on recognising symptoms of hypoglycaemia,
  - structured educational and psycho-behavioural programs (e.g. Blood glucose awareness training) that may help to improve detection of hypoglycaemia and reduce the frequency of severe episodes.[470,471 (Level I)]
- Patients at risk of hypoglycaemia should be discouraged from driving motor-vehicles, cycling, swimming or operating heavy machinery, as these activities may endanger oneself and the public.

Treatment of hypoglycaemia

- The aims of treatment are to:
  - detect and treat a low plasma glucose level promptly,
  - eliminate the risk of injury to oneself and to relieve symptoms quickly; and
  - avoid over-correction of hypoglycaemia especially in repeated cases as this will lead to poor glycaemic control and weight gain.[40 (Level III)]
- In Level I and Level 2 hypoglycaemia the patient should ingest:[472,473 (Level II-3) 6,40,474 (Level III)]
  - 15 g of simple CHO e.g.
    - 1 tablespoon of honey,
    - 150-200 ml of fruit juice such as orange juice or regular soft drink; or
    - 3 teaspoons of table sugar dissolved in water.
  - Measure plasma glucose after 15 minutes.
  - If the level at 15 minutes is still <3.9 mmol/L, another 15 g of CHO should be taken.
  - People taking AGIs (acarbose) must use glucose (dextrose) tablets or, if unavailable, milk or honey to treat the hypoglycaemia.
- In Level 3 hypoglycaemia,[6,40,474 (Level III)]
  - where the individual is still conscious, administer 20 g of CHO and the above steps are repeated.
  - where the individual is unconscious, administer:
    - 20-50 ml of Dextrose (D) 50% intravenously (IV) over 1-3 minutes, or
    - 75-100 ml of D20% over 15 minutes, or
    - 1 mg glucagon subcutaneously (SC) or intramuscularly (IM).
    - Outside the hospital setting, a tablespoon of honey (or equivalent e.g. maple syrup) 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 recurrent hypoglycaemia.
- Evaluate cause of the hypoglycaemia and educate patient on how to prevent future episodes.
- Diabetes treatment (OGLDs and insulin) regime may need to be reviewed and adjusted.

Figure 4-1: Acute management of hypoglycaemia.



CHO: carbohydrate; IV: intravenous; IM: intramuscular.

Adapted from Kapoor N, et al. Curr Med Issues 2017.[475 (Level III)]

Hypoglycaemia unawareness

- Hypoglycaemia unawareness occurs when the ability to perceive the autonomic warning symptoms is either diminished or lost such that the first sign of hypoglycaemia is confusion or loss of consciousness.[40 (Level III)]
- Recent or recurrent hypoglycaemia can decrease normal responses to hypoglycaemia[476 (Level II-2)] and lead to defective glucose counter-regulation and hypoglycaemia unawareness.
- Hypoglycaemia unawareness increases the incidence of severe hypoglycaemia and therefore should trigger re-evaluation of the treatment regimen.[477 (Level III)]
- Both hypoglycaemia unawareness and defective glucose counter-regulation are potentially reversible.
- Patients should be advised to temporarily relax their targets.

- Strict avoidance of hypoglycaemia for 2 days-3 months has been associated with improvement in the recognition of severe hypoglycaemia, the counter-regulatory hormone responses or both.[40 (Level III) 478-483 (Level II-2)]

Nocturnal hypoglycaemia

- Risk of nocturnal hypoglycaemia is higher especially in the elderly.[334 (Level II-3)]
- The clinical manifestations may include:[40 (Level III) 484,485 (Level II-2)]
  - poor sleep quality,
  - vivid dreams or nightmares,
  - waking up with chills or sweating,
  - morning headache,
  - chronic fatigue,
  - mood changes,
  - nocturnal convulsions.
- Nocturnal hypoglycaemia may contribute to morning hyperglycaemia.
- Undetected nocturnal hypoglycaemia can promote:
  - hypoglycaemia unawareness,
  - blunt counterregulatory responses,
  - anxiety, reduce quality of life and increase treatment costs.[486 (Level II-3)]
  - negative outcomes such as falls, accidents and arrhythmias.
- To reduce the risk of asymptomatic nocturnal hypoglycaemia, individuals on basal insulin therapy should periodically monitor early morning (2-5 am, corresponding with the peak action time of the basal insulin) plasma glucose levels.[40 (Level III)]
  - Consider switching from human basal insulin to basal insulin analogues
- Patients on SU should readjust dose/consider switching to an OGLD without hypoglycaemia risk.

Complications of hypoglycaemia

- Hypoglycaemia can cause acute harm to the person with T2DM or others, especially if it causes falls, motor vehicle accidents, or other accidents.
- A large cohort study suggested that among older adults with T2DM, a history of severe hypoglycaemia was associated with greater risk of dementia.[487 (Level II-3)]
- Severe hypoglycaemia was associated with excess mortality in participants in both the standard and the intensive glycaemia arms of the ACCORD, VADT and ADVANCE trials.[488-491 (Level I)]

- In people with T2DM and established or very high risk for CVD, there is a clear association between severe hypoglycaemia and increased mortality.[492,493 (Level I) 494(Level II-3)]

- Acute hypoglycaemia is proinflammatory, increases platelet activation and decreases fibrinolysis, leading to a prothrombotic state.[495,496 (Level II-2)]

- Hypoglycaemia is associated with increased heart rate, SBP, myocardial contractility, stroke volume and cardiac output, and can induce ST- and T-wave changes with a lengthening of the QT interval (slower repolarization), which may increase the risk of arrhythmias and sudden cardiac death.[497-499 (Level II-2) 500 (Level II-3) 501 (Level III)]

Recommendations: Hypoglycaemia

1. Patients at risk of hypoglycaemia or with high CV risk should be educated to recognise and prevent hypoglycaemia.	*Grade C*
2. Patients on insulin/insulin secretagogues therapy should periodically monitor early morning glucose to detect nocturnal hypoglycaemia.	*Grade C*
3. Patients with hypoglycaemia unawareness and those with concomitant CVD should relax their glycaemic targets.	*Grade C*
4. Hypoglycaemia unawareness should trigger re-evaluation of the treatment regimen.	*Grade C*
5. Patients with hypoglycaemia unawareness should avoid hypoglycaemia for 2 days-3 months to regain early hypoglycaemia warning symptoms.	*Grade B*

4.2 Diabetic ketoacidosis

- Diabetic ketoacidosis (DKA) is among the most serious acute complications of T2DM.[502]
- It has a high mortality rate if unrecognised. The overall mortality is <1%, but a mortality rate >5% in the elderly has been reported.[502]
- Mortality in patients with DKA is frequently related to the underlying aetiological precipitant rather than the metabolic sequelae of hyperglycaemia or ketoacidosis.[502]

Principles of management

- Correction of dehydration
- Correction of electrolyte imbalance
- Insulin therapy
- Treatment of precipitating factor
- Prevention of complications

Assessment

- Initial assessment
  - › History and physical examination
    - Look for precipitating causes: infection, missed therapy, non-adherence, acute coronary syndrome, cerebrovascular accident, surgery and drugs (e.g. steroids).
  - › Investigations
    - Capillary and venous plasma glucose
    - Venous blood gas (pH, bicarbonate)
    - Blood or urinary ketones
    - BUSE and creatinine
    - FBC
    - Urinalysis
    - If indicated: blood cultures, CXR and ECG
- Diagnostic criteria
  - › All 3 criteria must be met[503] (Level III)
    - Capillary plasma glucose >11 mmol/L
    - Capillary ketones >3 mmol/L or urine ketones ≥2+
    - Venous pH <7.3 and/or bicarbonate <15 mmol/L

- Patients with high risk for DKA or severe DKA should be admitted to HDU or the ICU. High-risk factors include:
  - elderly
  - pregnancy
  - heart and kidney failure
  - other serious co-morbidities

- Clinical parameters for severe DKA
  - Venous bicarbonate <5 mmol/L
  - Plasma ketones >6 mmol/L
  - Venous pH <7.1
  - Hypokalaemia on admission (<3.5 mmol/L)
  - GCS <12
  - Oxygen saturation <92% on air (via arterial blood gases [ABG])
  - Systolic BP <90 mmHg
  - Pulse >100 beats/minute
  - Anion gap >16 (Anion gap = $[Na^+ + K^+] - [Cl^- + HCO_3^-]$)*

** Na+: sodium; K+: potassium; Cl- : chloride; HCO_3- : bicarbonate*

Treatment

- Aims of treatment
  - Rate of fall of ketones of at least 0.5 mmol/L/hr, **OR**
  - Bicarbonate rise of 3 mmol/L/hr, **AND**
  - Plasma glucose fall of at least 3 mmol/L/hr, **AND**
  - Maintain serum potassium within normal range.

- Precaution during treatment
  - Avoid over-correction of hyperglycaemia (within the first 12-24 hours of treatment, avoid lowering glucose to <14.0 mmol/L)

A. Immediate treatment

- Correction of dehydration
  - Fluid deficits in DKA may be up to 10% of total body weight. Restoration of circulating volume is a priority.[502]
  - **SBP on admission <90 mmHg** (likely due to low circulating volume, but consider other causes such as heart failure or sepsis).[503 (Level III)] Start administration of fluid as shown in Table 4-3.

Table 4-3: Correction of dehydration in DKA with admission SBP <90 mmHg.

SBP status	Action
SBP <90 mmHg **Remains <90 mmHg** **If fails to pick up**	Give 500 ml of 0.9% saline solution over 10-15 minutes. Repeat the above Consider colloids e.g. Gelafundin
SBP >90 mmHg	Give 1000 ml of 0.9% normal saline over the next 60 minutes.

Addition of potassium is likely to be required in the second litre of fluid, especially if baseline potassium is <5 mmol/L, and aim to maintain levels between 4-5 mmol/L.

› **SBP on admission is ≥90 mmHg,**[503 (Level III)] start administration of fluid as shown in Table 4-4.

Table 4-4: Correction of dehydration in DKA with admission SBP ≥90 mmHg.

Hours from admission	Action
First 1 hour	Start IV fluid 1L of 0.9% saline
	Continue fluid replacement via infusion pump depending on hydration status
Over next 2 hours **Over next 4 hours** **Over next 6-8 hours**	1000 ml of 0.9% saline with potassium chloride (KCl) 1000 ml of 0.9% saline with KCl 1000 ml of 0.9% saline with KCl

› The rate of hydration should be guided by:
- haemodynamic status,
- state of hydration,
- serum electrolyte levels; and
- urinary output.

› More cautious fluid replacement in:**
- young people <18 years
- elderly
- pregnancy
- existing heart or renal failure

*** In the above instances, consider HDU admission and, insertion and monitoring via central line.*

- Potassium replacement

› Aim to maintain serum potassium between 4-5 mmol/L.
› Withhold K^+ replacement if there is no urine output.

Table 4-5: Potassium replacement of infusion solution.

Potassium level (mmol/L)	Potassium replacement of infusion solution
>5.5	Nil
3.5-5.5	20-30 mmol KCl/l*
<3.5	additional K^+ replacement required**

**1 g KCl = 13.4 mmol K^+; ** Maximum potassium replacement per hour is 40 mmol/h.*

- Insulin
  - Start a fixed rate IV insulin infusion (FRIII): 0.1 unit/kg/hr based on estimate of weight.[503 (Level III)]
  - 50 units short-acting human insulin or rapid-acting insulin analogue[504 (Level II-2)] made up to 50 ml with 0.9% saline solution.
  - Delay insulin infusion if the initial potassium <3.5 mmol/L until serum potassium is corrected.
  - Basal insulin – may consider continuing patient's SC long-acting analogue/ human insulin while on IV insulin infusion.[505,506 (Level II-1)]
  - Monitor capillary glucose hourly – if the glucose does not fall by at least 3 mmol/L/hr in the first 2-3 hours despite adequate hydration, increase FRIII by 1 U/hr.
  - Once plasma glucose falls below 14 mmol/L: [503(Level III)]
    - add or switch to 5% dextrose and reduce insulin infusion rate by 50%,
    - in the presence of persistent ketonaemia, consider maintaining insulin infusion rate and changing to 10% dextrose.
  - Beyond 24 hours, maintain plasma glucose at 8-12 mmol/L.[503 (Level III)]
- IV bicarbonate
  - The use of IV HCO_3^- is not indicated to correct acidosis in DKA due to:
    - rise of partial pressure of carbon dioxide (pCO_2) in cerebrospinal fluid (CSF) which may lead to a paradoxical increase in CSF acidosis,
    - delay in the fall of plasma lactate and ketone level; and
    - risk of cerebral oedema especially in younger age group.
  - While evidence is lacking, IV HCO_3^- may be considered if pH is persistently <6.9 despite adequate hydration and insulin treatment.[502 (Level III)]
    - E.g. 1 ampoule (50 ml) 8.4% $NaHCO_3$ added to 200 ml D5% over 1 hr, repeated every 1-2 hours, until pH is ≥7.0.[502 (Level III)] *Each ml of 8.4% $NaHCO_3$ solution contains 84.0 mg $NaHCO_3$ (e.g. 1.0 mmol/ml).*
- Phosphate
  - No evidence to support routine phosphate replacement for DKA.[502 (Level III)]
  - If levels <0.32 mmol/L in the presence of cardiac dysfunction or respiratory depression, consider phosphate replacement.

B. Monitoring

- Hourly capillary plasma glucose until it reaches maintenance level of 8 mmol/L-12 mmol/L, then monitor 2-4 hourly.
- Vital signs and input-output charting hourly
- Venous HCO_3^- and K^+ at 60 minutes, 4 hours and 6-hourly thereafter
- 6-hourly BUSE and blood/urine ketones
- If ketones and glucose are not falling as expected, check if the insulin infusion pump is working and connected, and the correct insulin residual volume is present.
- If equipment is working but response to treatment inadequate, increase insulin infusion rate by 1 U/hr increments hourly until targets are achieved.

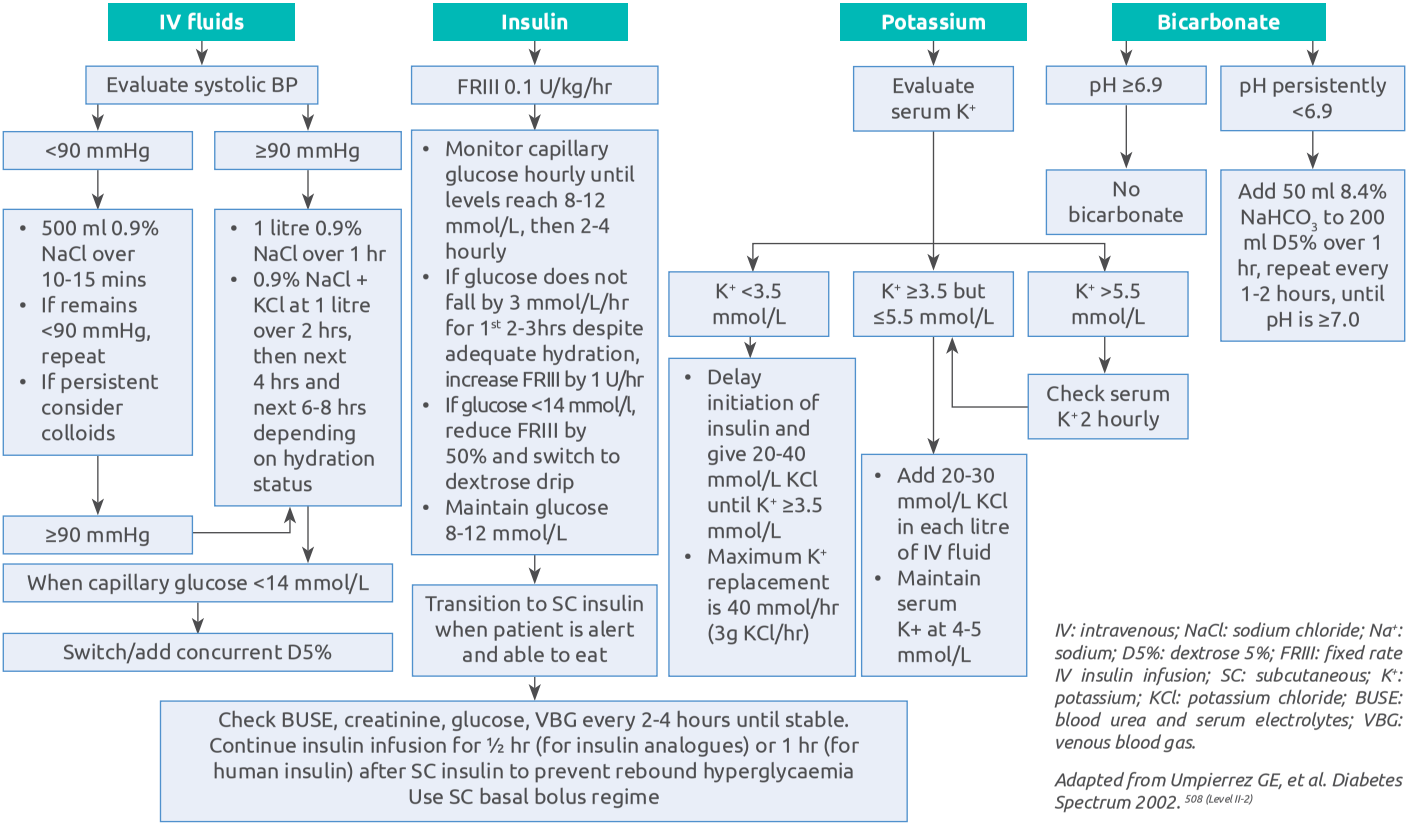
C. Resolution

- Continue IV insulin infusion until resolution of DKA
- Resolution is defined as:[505 (Level III)]
  - pH >7.3
  - Plasma ketone <0.6 mmol/L

D. Transitioning from IV insulin to SC basal bolus insulin

- Patient should be eating and drinking, and back on normal insulin.[505 (Level III)]
- Overlap the SC insulin with the insulin infusion for ½ hour (for insulin analogues) or 1 hour (for human insulin).
- Calculating a basal bolus regimen (4 times daily)[503 (Level III)]
  - Current practice is shifting away from estimating total daily dose (TDD) of SC insulin based on the last 12-24-hour-insulin administered.[507 (Level III)]
  - Estimate total daily dose (TDD) of insulin by multiplying the patient's weight (in kg) by 0.5 U-0.75 U.
  - Use 0.75 U/kg for those considered to be more insulin resistant e.g. obese and/or presence of acanthosis nigricans.
  - Give 50% of TDD at bedtime in the form of long acting insulin and divide remaining dose equally between pre-breakfast, pre-lunch and pre-dinner meals.
- For patients already on insulin before admission, consider resuming previous insulin regimen and adjust dose as needed.
- Monitor and adjust insulin doses accordingly.

Figure 4-2: Algorithm for management of T2DM with DKA.



IV: intravenous; NaCl: sodium chloride; Na^+: sodium; D5%: dextrose 5%; FRIII: fixed rate IV insulin infusion; SC: subcutaneous; K^+: potassium; KCl: potassium chloride; BUSE: blood urea and serum electrolytes; VBG: venous blood gas.

Adapted from Umpierrez GE, et al. Diabetes Spectrum 2002. [508 (Level II-2)]

4.3 Euglycaemic ketoacidosis

- Approximately 10% of patients with DKA present with near-normal glycaemic values.[509]
- The current definition for euglycaemic ketoacidosis is plasma glucose level <11.0 mmol/L.[510,511 (Level III)]
- Euglycaemic ketoacidosis has been described in T1DM[509] and in pregnancy.[512,513]
- Recently there has been an increasing number of cases of euglycaemic ketoacidosis associated with the use of SGLT2-i for treatment of T2DM.[514 (Level II-2)]
  - › Hence, a normal or mildly elevated plasma glucose does not rule out DKA in pregnancy or with SGLT2 inhibitor use.
  - › The documented precipitating factors in patients on SGLT2-i include acute illnesses (such as infection), recent major surgery and insulin dose reduction or omission.[515 (Level I) 516 (Level II-2)]
- Clinical presentation is similar to ketoacidosis. Although the definition states that random plasma glucose is <11.0 mmol/L, most patients' plasma glucose are elevated to >11.0 mmol/L but, lower than levels associated with DKA (~15 mmol/L-17 mmol/L).
  - › A high index of suspicion is required for its timely diagnosis because of the absence of very high glucose levels as seen classically in patients with DKA.
  - › When patients present (whether at outpatient clinics/emergency wards or as in-patients),
    - where there has been poor oral intake/prolonged fasting e.g. during Ramadan/have an acute illness/are post-operative,
    - check for a history of taking SGLT2-i,
    - make it a routine to check for ketones (urine/blood) and if necessary, blood gas and anion gap – to prevent delay in making a timely diagnosis and institute appropriate emergency management.
- Treatment should follow standard DKA management protocol except dehydration is corrected with 5% dextrose saline or 5% dextrose.[509 (Level III)]
  - › When the plasma glucose is low in the absence of clinical dehydration, 10% dextrose may be required.
- SGLT2-i should be withheld and restarted when ketoacidosis resolves and patient is tolerating oral food intake. [511 (Level III)]

4.4 Hyperglycaemic hyperosmolar state (HHS)

- Hyperglycaemic hyperosmolar state (HHS) is a life-threatening emergency and should be suspected in patients with T2DM who are very ill with significant hyperglycaemia.
- Can be an initial presentation of undiagnosed T2DM (7-17%).
- Diagnosis of HHS must be prompt and managed intensively in HDU or equivalent level of care.[517 (Level III)]
- The elderly with multiple co-morbidities are prone to HHS.[518,519 (Level II-3)]
- It has a higher mortality than DKA and vascular complications such as MI, stroke or peripheral arterial thrombosis are common.[518-521 (Level II-3)]
  - Well-described complications such as seizures, cerebral oedema and osmotic demyelination syndrome though uncommon[522 (Level III)] can occur due to rapid changes in osmolality during treatment.[523 (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 profound.[524 (Level III)]

Diagnostic criteria[517 (Level III)]

- Severe dehydration
- Marked hyperglycaemia (plasma glucose >30 mmol/L)
- Serum osmolality >320 mosmol/kg
  - Effective serum osmolality = 2 (Na^{2+}) [mmol/L] + glucose [mmol/]
  - In severe hyperglycaemia, measured serum Na^{2+} is falsely low i.e. pseudohyponatremia. Recognition of pseudohyponatraemia is important to avoid use of hypertonic saline during fluid management.
  - Urea levels are not used for calculation of osmolality, as it passes freely across the plasma membranes and its accumulation does not induce an osmotic gradient across cell membranes.[525]

Other important clinical features[517] *(Level III)*

- There is no significant ketonaemia (<3.0 mmol/L) or acidosis (pH >7.3, HCO_3^- >15 mmol/L).
- When significant acidosis is present, a mixed picture of HHS and DKA should be considered. However, other causes of acidosis (such as lactic acidosis, sepsis and poisoning) should be excluded.
- If there is worsening of acute cognitive impairment, consider:
  - › cerebral oedema in severe cases or 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.
- Precipitating factors for HHS[526,527] (Level III)
  - › Infection (30-60%)
  - › Poor adherence to treatment – omission of insulin or OGLDs
  - › Presence of acute concomitant illness – cerebrovascular events, myocardial infarction
  - › Medication – diuretics, glucocorticoids or antipsychotic drugs

Management goals

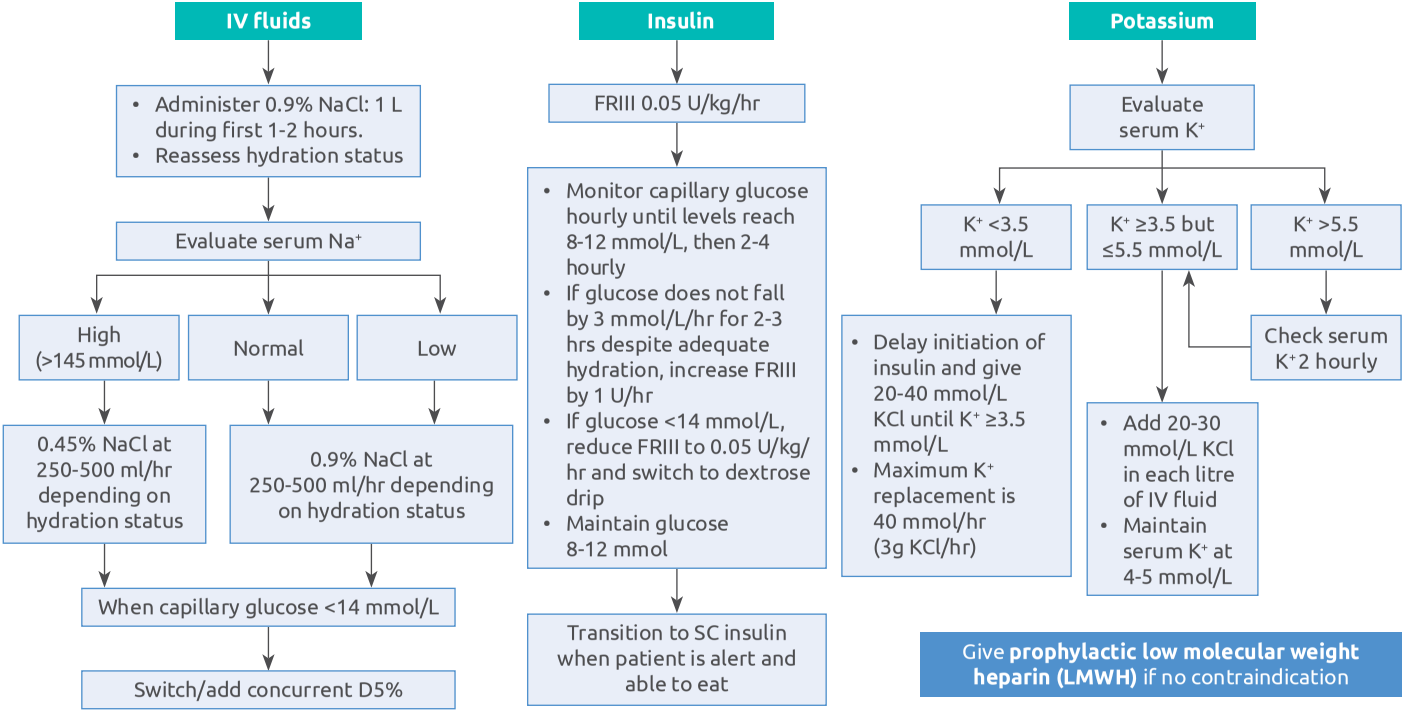
- The treatment goals of HHS are to treat the underlying cause as well as gradual and safe:
  - › correction of dehydration,
  - › correction of electrolyte imbalance,
  - › control of hyperglycaemia,
  - › treatment of precipitating factors,
  - › prevention of complications.

Principles of treatment

- IV 0.9% saline solution is the principle fluid to restore circulating volume and correction of dehydration.
- IV 0.45% saline solution is used if serum Na^{2+} is >145 mmol/L or the serum osmolality is not declining (<3 mosm/kg) despite adequate hydration.

- Recognition of pseudohyponatraemia in severe hyperglycaemia is important as to avoid using hypertonic saline.
- Most algorithms[6,40] recommend use of corrected Na^{2+} after restoring circulatory volume, however, in general use of measured Na^{2+} is acceptable to guide decision on fluid management.
- In the presence of heart failure and renal failure, cautious fluid replacement is advised.
- Aim for gradual reduction in serum osmolality at the rate of 3-8 mosm/kg/hr.
- An initial rise in Na^{2+} is expected and is not in itself an indication for hypotonic fluids. Thereafter, the rate of fall of plasma Na^{2+} should not exceed 10 mmol/L in 24 hours.
- Too rapid fall in glucose should be avoided.
  - › Aim for a reduction in blood glucose of 4-6 mmol/L/hr.[505 (Level III)]
- Prophylactic low molecular weight heparin (LMWH) is recommended unless contraindicated.
- Identify and treat the precipitating cause.
- Resolution of HHS is when the patient is alert, eating well, serum osmolality <320 mosm/kg and plasma glucose level <14 mmol/L.[502,527 (Level III)]
- Once HHS resolves, transition from IV insulin to SC basal bolus insulin. However, patients with HHS are more insulin sensitive and may require lower insulin dose.
- To reduce the risk of recurrence and prevent long-term complications, discharge planning should include:
  - › diabetes education,
  - › dietitian referral,
  - › education on medications including insulin administration, if required.

Figure 4-3: Algorithm for management of T2DM with HHS.



IV: intravenous; NaCl: sodium chloride; Na^+: sodium; D5%: dextrose 5%; FRIII: fixed rate IV insulin infusion; SC: subcutaneous; K^+: potassium; BUSE: blood urea and serum electrolytes; VBG: venous blood gas.

Adapted from Umpierrez GE, et al. Diabetes Spectrum 2002. [508 (Level II-2)]

Recommendations: DKA and 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*

SECTION 5

MANAGEMENT OF CHRONIC COMPLICATIONS

5.1 Retinopathy

SUMMARY OF UPDATES

- Anti-vascular endothelial growth factor (anti-VEGF) therapy has emerged as the treatment of choice in centre-involving diabetic macular oedema, shown to be superior to laser photocoagulation in improving vision.
- Rapid improvement of glycaemia in patients with established retinopathy may be associated with transient worsening of retinopathy. Co-management with an ophthalmologist and a more gradual improvement of glycaemia is advised.

- Prevalence of diabetic retinopathy is closely linked to duration of diabetes and level of glycaemic control.[528 (Level II-2) 529 (Level I)]
- Other factors that increase risk of retinopathy include hypertension and nephropathy.[530 (Level II-3) 531 (Level II-2)]
- 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.[532 (Level III)]
- Diabetic retinopathy is the leading cause of blindness among adults in developed countries.
  - In Malaysia, the prevalence of diabetic retinopathy from the 2007 Diabetes Eye Registry was 36.8%.[533 (Level III)]
  - More recently, a prevalence of retinopathy in ambulatory outpatients with T2DM of 15% and 39.3% was found in Klang Valley and Kelantan tertiary care centres respectively.[534,535]

Screening

- Screening and early treatment can prevent substantial visual loss in many cases.[536 (Level II-3) 537 (Level II-2)]
- Screening should include:
  - › visual acuity assessment using Snellen or equivalent chart with pinhole correction,
  - › a non-mydriatic fundus camera photography as a part of a telemedicine program with remote review by credentialled personnel.[538,539 (Level III)]
- In general, eye examinations are repeated every 1-2 years in those with minimal-to-no retinopathy.[536 (Level II-3) 537 (Level II-2)]

Eye examination

- Ideally at the time of diagnosis of T2DM and preferably performed by an ophthalmologist.[540 (Level I)]
- Should include:
  - › visual acuity assessment using Snellen or equivalent chart with pinhole correction, and
  - › complete anterior segment and dilated fundus examination.

In low-/intermediate resource settings, screening should include visual acuity assessment and retinal examination for adequate Diabetic Retinopathy Classification by trained/credentialled personnel.[538 (Level III)]

Management

A. Delay onset and progression

- Glucose
  - › Intensive glucose-lowering has been shown to prevent and/or delay onset and progression of retinopathy in T2DM.[401, 541,542 (Level I)]
  - › In situations where rapid control of glucose is expected in patients with pre-existing diabetic retinopathy there is a potential for transient worsening of retinopathy hence, referral for detailed ophthalmological assessment is required.[259,260,543 (Level I) 544-546 (Level II)]
    - If diabetic retinopathy is documented, care should be taken when improving glycaemic control and patients need to be counselled regarding the likelihood of transient worsening of retinopathy.
- Blood pressure
  - › Lowering blood pressure (BP) decreases retinopathy progression, although lowering BP intensively (systolic BP <120 mmHg) does not impart additional benefit.[401,547,548 (Level I)]

- Fenofibrate use
  - Retinopathy progression may be slowed by addition of fenofibrate particularly in those with non-proliferative diabetic retinopathy (NPDR).[400,401 (Level I)]
  - This holds true irrespective of baseline dyslipidaemia status.
- Aspirin use
  - 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.[549 (Level I)]

B. Treatment

- Photocoagulation therapy
  - Laser photocoagulation remains the standard practice for treating diabetic retinopathy. Laser therapy is indicated for severe NPDR and proliferative diabetic retinopathy.[550 (Level I)]
  - Laser therapy is only relatively indicated in certain types of diabetic macular oedema.[551 (Level III)]
- Anti-vascular endothelial growth factor (anti-VEGF)
  - Vascular endothelial growth factor (VEGF) plays an important role in diabetic retinopathy, particularly in the development of diabetic macular oedema.
  - Anti-VEGF therapy is superior to laser photocoagulation,[552 (Level I)] improves vision and is the treatment of choice in centre-involving diabetic macular oedema.[553 (Level I)]
  - Potential adverse effects of anti-VEGFs include transient increases in intraocular pressure and injection-related infectious endophthalmitis.[554 (Level I)]
  - Non-ocular adverse events reported include cerebrovascular accidents and MI. However systematic reviews have not found a statistically significant association.[552 (Level I)]

Referral to ophthalmologist

- Referral to an ophthalmologist is necessary for the following situations (Refer Table 5-1):
  - severe NPDR,
  - any level of diabetic maculopathy,
  - any proliferative diabetic retinopathy,
  - unexplained visual loss,
  - if screening examination cannot be performed, or ungradeable fundus photo is used.

Table 5-1: Recommended follow-up and referral schedule for diabetic retinopathy.

Stage of retinopathy	Follow-up
No DR	12-24 months
Mild NPDR without maculopathy	9-12 months
Moderate NPDR without maculopathy	6 months
Mild/moderate NPDR with maculopathy	Refer ophthalmologist
Severe NPDR without maculopathy	
Any maculopathy	
Proliferative DR	Refer urgently to ophthalmologist
Advanced diabetic eye disease (ADED)	

DR: diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy. Colours indicate progressive urgency for referrals (Refer Table 5-2 for criteria for urgent referrals).

Adapted from Malaysian CPG for Screening of Diabetic Retinopathy, 2011.[539 (Level III)]

Table 5-2: Criteria for urgent referral.

Urgency of referral	Ocular features
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

NPDR: non-proliferative diabetic retinopathy.

Adapted from Malaysian CPG for Screening of Diabetic Retinopathy, 2011.[539 (Level III)]

Recommendations: Retinopathy

1. Improving glycaemic control and optimising BP reduces risk of development and progression of retinopathy.	*Grade A*
2. In T2DM, screening and evaluation for retinopathy is indicated at the time of diagnosis.	*Grade B*
3. The interval for follow-up assessment should be decided based on severity of retinopathy.	*Grade C*
4. In those without retinopathy the recommended interval is 1-2 years.	*Grade B*
5. Pan-retinal laser photocoagulation is indicated to reduce visual loss in high risk proliferative diabetic retinopathy and in some cases, severe non-proliferative retinopathy.	*Grade C*
6. Intra-vitreal anti-VEGF is indicated for sight-threatening centre-involving diabetic macular oedema.	*Grade A*

5.2 Diabetic kidney disease (DKD)

SUMMARY OF UPDATES

- DKD is the new term used to refer to kidney disease caused by T2DM.
- SGLT2-i have been proven to be renoprotective, beyond glucose-lowering.
- SGLT2-i should be considered in patients with albuminuria and DKD down to eGFR 30 ml/min/1.73 m^2, to reduce DKD progression.
- GLP1-RA have been shown to reduce albuminuria progression in DKD with high CV risk.

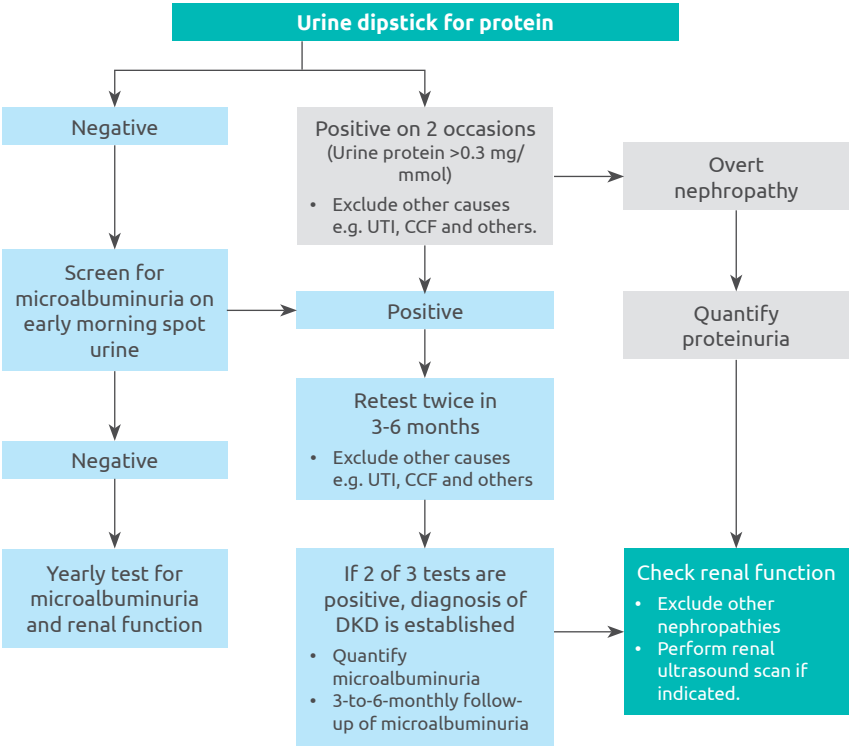
- DKD is a major cause of chronic kidney disease and may be present at diagnosis of T2DM, and can progress to ESKD.[555 (Level II-3)]
- It accounted for 65% of new patients requiring dialysis in Malaysia in 2016.[5 (Level II-3)]
- DKD markedly increases CV risk and healthcare costs.[556 (Level I) 557 (Level II-2)]
- Diagnosis is made clinically – based on presence of albuminuria and/or reduced eGFR in the absence of other causes of kidney disease.[558 (Level III)] If there is concomitant presence of other microvascular complications (e.g. retinopathy), it is more suggestive that the albuminuria/reduced eGFR is due to DKD.
- Progression to ESKD requiring renal replacement therapy (RRT) occurs in many with poorly controlled BP and glucose.

Screening and risk stratification

- Screening should encompass:
  - assessment of albuminuria,
  - estimation of glomerular filtration rate (eGFR).
- DKD can be present with or without albuminuria, in the presence or absence of retinopathy.[559,560 (Level II-2)]

A. Assessment of albuminuria

Figure 5-1: Assessment of albuminuria.



UTI: urinary tract infection; CCF: congestive cardiac failure; DKD: diabetic kidney disease.

Adapted from Malaysian CPG on Management of Chronic Kidney Disease, 2018.[561 (Level III)]

- A standard urine dipstick test should be performed at diagnosis of T2DM and annually.[561 (Level III)]
- A positive dipstick test should be confirmed on two occasions within 3 months.
- Albuminuria should be quantified, if present.
- If dipstick is negative, screen for urine microalbuminuria (first morning sample or a random sample without excessive water intake).[561 (Level III)] If microalbuminuria is negative, test yearly.
- Moderately increased albuminuria (previously known as microalbuminuria) is the earliest sign of DKD and predicts increased CV mortality and morbidity and ESKD.[556 (Level I)]

- If albuminuria is detected, repeat the test twice in 3-6 months for confirmation[561] (Level III) after excluding other causes such as UTI and CCF. If 2 out of 3 tests are positive, a diagnosis of DKD is established.
- Albuminuria may be affected by variation in urine concentration due to hydration.
- If microalbuminuria dipstick is positive, it is recommended to do a more specific test urine albumin- creatinine ratio (UACR). The UACR is not affected by urine concentration and should be done early morning to minimise effect of posture and exercise.[562] (Level III)
- UACR >3.0 mg/mmol is equivalent to >30 mg protein excretion/24 hours and should be monitored at least twice yearly (Refer table 5-3 for stratifying albuminuria status according to ACR/AER).

Table 5-3: Stages of CKD based on albuminuria

				Persistent albuminuria categories		
				A1	A2	A3
				Normal-to-mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²)	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly-to-moderately decreased	45-59			
	G3b	Moderately-to-severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Renal failure	<15			

Colours indicate prognosis - Green: low risk; Yellow: moderate risk, Orange: high risk, Red and deep red: very high risk. GFR: glomerular filtration rate.

Adapted from KDIGO 2020 CPG for Diabetes Management in Chronic Kidney Disease. [956] (Level III)

Recommendations: Screening for DKD

1. DKD should be assessed, risk stratified and managed based on degree of albuminuria and eGFR.	*Grade C*
2. Screening for albuminuria should be performed at diagnosis and annually with a conventional dipstick on an early morning urine specimen.	*Grade C*
3. If urine dipstick for albuminuria is negative, screening for microalbuminuria should be performed.	*Grade C*
4. If microalbuminuria is detected, confirmation should be made with a repeat test within 3 to 6 months.	*Grade C*
5. If microalbuminuria is not detected, re-screening should be performed annually.	*Grade C*
6. Regardless of the degree of albuminuria, serum creatinine level should be measured annually to determine GFR based on the CKD EPI formula.	*Grade C*

Management

A. General management

- Preventing progression of DKD encompasses:
  - › BP control,
  - › glycaemic control,
  - › RAS blockade,[24,373,567-569 (Level I) 355 (Level III)]
  - › SGLT2 inhibition.[201,202,209,589,955 (Level I)]
- Dose adjustments of GLDs may be necessary with eGFR <60ml/min/1.73 m^2. (Refer Appendix 7)
- BP control
  - › BP targets
    - BP target in DKD should be <130/80 mmHg regardless of level of albuminuria.[561 (Level III) 570 (Level II-1) 571 (Level II-2)]
    - SBP should not be <120 mmHg and DBP not <70 mmHg.

- ACE inhibitors/ARB
  - ACE inhibitor or ARB is the preferred first-line agent for BP in DKD with proven benefit on prevention of DKD progression, via their anti-proteinuric effects.[372,373,572 (Level I)]
  - ACE inhibitor or ARB is beneficial in DKD with albuminuria even when BP is <130/80 mmHg.[371,373,561,573-576 (Level I)]
  - Normalisation of microalbuminuria is associated with a reduction in the rate of decline of GFR.[371 (Level I)]
  - Urine protein-creatinine ratio (uPCr) or UACR should be used to monitor treatment response directed against proteinuria. uPCR is preferred in those with established proteinuria in view of its cost-effectiveness.[577 (Level III)]
  - ACE inhibitor and ARB are similar in terms of benefits and risks.[370 (Level I) 578 (Level II-2)]
  - Renal profile should be reassessed within 2-4 weeks upon initiation or dose escalation of ACE inhibitor/ARB therapy, especially in patients with impaired renal function at baseline.
  - Consider reducing dose or discontinuing ACE inhibitor/ARB within 2 months upon commencement (after excluding other precipitating factors) when:[561 (Level III)]
    - serum creatinine levels remain ≥30% from the baseline; or
    - eGFR reduces ≥25%; or
    - serum potassium ≥5.6 mmol/L.
  - ACE inhibitor/ARB should be titrated to the maximum recommended dose to achieve optimal BP targets and anti-proteinuric effects.[561 (Level III)]
  - The benefits and risks of withholding RAS blockers in advanced DKD are debatable. There is an ongoing trial to assess this.[579 (Level I)]
  - Combination of ACE inhibitor with ARB should not be used routinely. This combination showed no added benefit but had higher adverse effects such as hyperkalaemia and acute kidney injury.[580 (Level I) 581 (Level II-1)]
- Mineralocorticoid antagonist
  - Finerenone, a selective mineralocorticoid antagonist has recently been shown to reduce DKD progression and CV events in DKD.[954 (Level I)]
  - Mineralocorticoid receptor antagonists (spironolactone, eplerenone and finerenone) in combination with ACE inhibitor/ARB are effective for management of resistant hypertension and have been shown to reduce albuminuria in short-term studies of DKD, and may have additional CV benefits.[582 (Level I) 583 (Level II-2) 584 (Level II-1) 585 (Level III)]
  - Careful monitoring for hyperkalaemia is required when used in combination with ACE inhibitor/ARB.

- Glucose lowering
  - › Metformin
    - Metformin remains the first-line glucose-lowering therapy in DKD, unless eGFR <30 ml/min/1.73m^2.[586 (Level I)]
    - Dose reduction of metformin by 50% is required between eGFR 30-59 ml/min/1.73m^2.
  - › SGLT2-i
    - SGLT2-i reduce intraglomerular pressure, albuminuria and slow GFR decline independent of their glucose and BP lowering effects.[587 (Level III) 588 (Level I)]
    - SGLT2-i reduce the rate of DKD progression in patients up to eGFR 30-25 ml/min/1.73 m^2 [201,202,209,589,955(Level I)] despite lower anti-hyperglycaemic efficacy.
    - Do not initiate at eGFR <30 ml/min/1.73 m^2 – but, may continue if already initiated.[209,955 (Level I), 956 (Level III)]
    - Stop SGLT2-i when patient is initiated on dialysis.[956 (Level III)]
    - Patients with higher degree of albuminuria and advanced DKD benefitted the most.[209 (Level I)]
  - › GLP1-RA
    - GLP-1RA can be considered in patients with DKD and high CV risk in order to reduce albuminuria progression.[230,259,590 (Level I)]
    - Dedicated renal outcome trials with GLP1-RA are ongoing.[591]

- Protein and salt intake
  - › Maintain dietary protein at 0.8g/kg body weight/day[956 (Level III)] in DKD stage 3-5 (not on dialysis) while ensuring adequate energy intake (30-35 kcal/kg/day).[558,561,592 (Level III) 593 (Level I)]
  - › Dietary protein restriction may delay progression of renal impairment.
  - › Control of dietary potassium is important in those who are at risk of hyperkalaemia.[594 (Level III)]
  - › Salt restriction to <2 g/day (sodium chloride <5 g/day)[956(Level III)] is recommended to control BP and reduce CV risk.[595 (Level II-1)]

B. Other measures

- Lipid control (Refer Sub-section 3.9.2)
- Smoking cessation
- Weight reduction (Refer Sub-section 3.9.3)

Recommendations: Management of DKD

1. Optimise glucose and blood pressure control and use RAS blockade to slow progression of DKD.	*Grade A*
2. BP target should be ≤130/80 mmHg (SBP not <120 mmHg and DBP not <70 mmHg) in DKD regardless of level of albuminuria.	*Grade A*
3. ACEIs or ARBs should be initiated in patients with albuminuria, regardless of BP, as tolerated.	*Grade A*
4. SGLT2-i should be considered in patients with eGFR ≥30ml/min /1.73m^2, particularly in those with albuminuria to reduce risk of DKD progression.	*Grade A*
5. GLP1-RA should be considered in patients with DKD and at high CV risk.	*Grade A*

Referral to nephrologist

All patients with T2DM and DKD should be referred to a nephrologist in these situations:[561,565 (Level III)]

- rapid decline in renal function (eGFR loss >5 ml/min/1.73 m^2 in 1 year or >10 ml/min/1.73 m^2 in 5 years),
- eGFR <30 ml/min/1.73 m^2,
- persistent heavy proteinuria (≥1 g/day) despite optimal treatment,
- persistent haematuria with albuminuria (urine protein ≥0.5 g/day),
- other suspected causes apart from DKD (glomerular, genetic or uncertain cause),
- difficult to manage complications of DKD (anaemia, electrolyte disturbance including persistent hyperkalaemia, renal bone disease),
- resistant hypertension (failure to control BP despite 3 anti-hypertensive agents, including a diuretic),

- suspected renal artery stenosis,
- pregnant or planning for pregnancy.

Consultation with a nephrologist at eGFR <30ml/ min/1.73m^2 has been shown to delay dialysis, improve quality of care and reduce cost.[596 (Level III)] The reason for limiting referral to this eGFR is for purely logistical concerns. It is important for primary care and general physicians to jointly manage patients with nephrologists.

5.3 Neuropathy

SUMMARY OF UPDATES

- CV autonomic neuropathy is an independent risk factor for CV mortality.

- The diabetic peripheral neuropathies (DPN) are heterogeneous with diverse clinical manifestations. They may be diffuse or focal.[597]
- Diffuse neuropathies are:[597]
  - › distal symmetric polyneuropathy (DSPN), and
  - › diabetic autonomic neuropathy (DAN) particularly CV autonomic neuropathy.
- Focal neuropathies include:[597]
  - › mononeuritis, and
  - › radiculopathies.

Diabetic symmetric polyneuropathy (DSPN)

- The likelihood of having DSPN is higher in the presence of:[598]
  - › neuropathic symptoms,
  - › absent or decreased ankle reflex,
  - › decreased distal sensation,
  - › distal muscle weakness or atrophy, and
  - › abnormal nerve conduction study.

A. Screening and diagnosis

- DSPN should be assessed with a 10-g monofilament (starting from the dorsum of hallux, then moving proximally); and one other modality:
  - pin prick,
  - vibration sense using a 128-Hz tuning fork,
  - ankle reflexes; or
  - vibration perception threshold testing using a biothesiometer.

  These increase the sensitivity of detecting DSPN by 87%.[599-602 (Level II-3)]
- These bedside tests should be performed at least annually.[597 (Level III)]
- Consider screening for people with prediabetes/T2DM who have symptoms of peripheral neuropathy.
- In most cases, DSPN can be diagnosed clinically and electrophysiological tests are rarely required. Electrophysiological tests can be considered if there are atypical features:[597 (Level III)]
  - rapid onset or progression of neuropathy,
  - asymmetrical neuropathy,
  - predominantly motor neuropathy,
  - if other causes are considered; or
  - in cases of diagnostic uncertainty.
- Symptoms of neuropathic pain include:[603]
  - burning pain,
  - painful cold, electric shock-like pain
  - tingling pain, or
  - sensation of pins and needles, and
  - may be associated with paraesthesia, dysesthesia, or allodynia.
- Validated questionnaires are available to assess for neuropathic pain due to DSPN. However, these are for screening rather than diagnosis and include:
  - painDETECT[604]
  - DN4[605]
  - LANSS Pain Scale[606]
  - ID pain[607] (Refer Malaysian Association for the Study of Pain's Management of Neuropathic Pain (2nd edition), 2012. Available at: *http://www.masp.org.my/index.cfm?menuid=21*)

Of the above, DN4 and ID pain are simple and feasible for use in clinical practice, whilst LANSS Pain Scale and painDetect is more detailed and more frequently used for research purposes.

B. Management

- Intensive lifestyle intervention
  - › In T2DM, reduces the risk of DSPN.[608 (Level II-1)]
  - › In prediabetes, reduces the risk of DSPN especially in the subgroup that did not progress to T2DM.[609 (Level II-2)]
- Intensive glycaemic control has been shown to have a modest effect on reducing the risk of DSPN in people with T2DM.[610 (Level II-1)]
- No pharmacologic therapy has been shown to be effective in treating DSPN. However, there are drugs approved for pain associated with DSPN (Refer Table 5-4).
- Combination therapy of 2 medications may be more effective than higher doses of either medication as monotherapy.[611 (Level I)]
- Tricyclic antidepressants carry a higher risk of sedation and/or orthostatic hypotension and should be used with caution in older people at risk of falls.[612 (Level II-1)]
- Opioids carry a high risk of sedation, dependence, and other side-effects, hence should only be used in combination with other agents, instead of as first-line treatment for pain due to DSPN.
  - › The efficacy of tramadol is likely due to its serotonin and noradrenaline uptake blocking effect.
- Consider referring patients to pain specialists (if available), in particular if they require long-term opioid treatment.[597 (Level III)]

Table 5-4: Drugs approved for painful DSPN.

Class of drugs	Generic name	Adverse events	Issues	Dose in renal impairment[613] (Level III)
Voltage-gated calcium channel α2-δ subunit ligand	Pregabalin[614-616] Level I) Initial dose: 75mg OD or BD Effective dose: 150-300 mg BD Max dose: 600 mg/day in divided doses	Somnolence, dizziness, ataxia, seizure upon rapid withdrawal	• Pregabalin requires 2 weeks to achieve maximum efficacy, regular dosing is required during titration phase	eGFR 15-30: 25-150 mg/day in 1-2 divided doses eGFR <15: 25-75 mg OD
	Gabapentin[617] (Level I) Initial dose: 100-300 mg OD-to-TDS Effective dose: 900-3600 mg/day Max dose: 3600 mg/day in divided dose		• Efficacy of gabapentin at lower-to-intermediate dose is variable and often require higher dose	eGFR 30-50: 300-900 mg/day in 3 divided doses eGFR 15-29: 300-600 mg/day in 3 divided doses eGFR <15: 100-300 mg OD[618] (Level III)
Serotonin-norepinephrine reuptake inhibitor	Duloxetine[619-621] (Level I) Initial dose: 30 mg OD Effective dose: 60-120 mg OD Max dose: 120 mg OD	Nausea, somnolence, dizziness, dry mouth, constipation, hyponatremia, arrhythmia, seizures, serotonin syndrome	None	Consider lower starting dose and slow titration eGFR <30: Not recommended

Tricyclic antidepressant	Amitriptyline[622-624 (Level I)] Initial dose: 10-25 mg OD Effective dose: 25-100 mg/day Max dose: 150 mg/day	Somnolence, dizziness, insomnia, dry mouth, orthostatic hypotension, urinary retention, constipation, hyponatremia, arrhythmias, seizures, neuroleptic malignant syndrome	Side-effects of tricyclic antidepressants increase the risk of falls in older people.	No dose reduction but, increased likelihood of anticholinergic adverse events (blurred vision, dry mouth and constipation)
Opioid	Tapentadol[625,626 (Level I)] Initial dose: 50 mg BD Effective dose: 50 mg BD Max 500 mg/day	Somnolence, dizziness nausea, vomiting, constipation, respiratory depression, serotonin syndrome	Long-term use of opioid is associated with tolerance and dependence.	Avoid use or reduce dose as effects of opioids are increased and prolonged due to increased cerebral sensitivity in renal impairment • Tramadol and Oxycodone: As above • Tapentadol: No dose adjustment in mild-moderate renal impairment. Avoid in severe impairment
	Tramadol[627 (Level I)] Initial dose: 50 mg OD-to-BD Effective dose: 100-200 mg/day Max dose: 400 mg/day			
	Oxycodone[628 (Level I)] Initial dose: 5-10 mg BD			

Drugs approved for DSPN according to class preference.
eGFR is in mL/min/1.73 m^2
DSPN: diabetic symmetric polyneuropathy, OD: daily; BD: twice daily; TDS: three times daily; FDA: United States Food and Drug Administration.

Adapted from Pop-Busui, et al. 2017;[597 (Level I)] Bril V, et al. 2018;[629 (level III)] British National Formulary, 2015.[613 (Level III)]

Diabetic autonomic neuropathy (DAN)

- Diabetic autonomic neuropathy (DAN) causes CV, GI, urogenital, and pseudomotor dysfunctions, as well as hypoglycaemia unawareness and abnormal pupillary function (Refer Table 5-5).[597]
- Of clinical relevance, cardiovascular autonomic neuropathy (CAN) is an independent risk factor for cardiovascular mortality.[597,630 (Level I)]

A. Symptoms and diagnosis

Table 5-5: Symptoms of DAN.

CAN	GI	Urogenital	Sudomotor
Resting tachycardia Abnormal blood pressure regulation • Non-dipping • Reverse dipping Orthostatic hypotension • Light-headedness • Weakness • Faintness • Visual impairment • Syncope Orthostatic tachycardia or bradycardia and chronotropic incompetence • Light-headedness • Weakness • Faintness • Dizziness • Visual impairment • Syncope Exercise intolerance	Gastroparesis • Nausea • Bloating • Loss of appetite • Early satiety • Postprandial vomiting • Brittle diabetes Oesophageal dysfunction • Heartburn • Dysphagia for solids Diabetic diarrhoea • Profuse and watery diarrhoea • Faecal incontinence • May alternate with constipation Constipation • May alternate with explosive diarrhoea	Bladder dysfunction • Frequency • Urgency • Nocturia • Hesitancy • Weak stream • Dribbling • Urinary incontinence • Urinary retention Male sexual dysfunction • Erectile dysfunction • Decreased libido • Abnormal ejaculation Female sexual dysfunction • Decreased sexual desire • Increased pain during intercourse • Decreased sexual arousal • Inadequate lubrication	Dry skin • Anhidrosis • Gustatory sweating

CAN: cardiovascular autonomic neuropathy; GI: gastrointestinal.

Adapted from Pop-Busui et al. Diabetes Care, 2017.[597]

- Diagnosis of CAN
  - › Use of standardised CV autonomic reflex tests (CART) is recommended for diagnosis.
  - › Commonly utilised tests are postural BP, heart rate (HR) variability upon standing and deep breathing at 6 breaths/min.
  - › The presence of 2 or more abnormal CART results is generally accepted as diagnostic.
  - › The presence of abnormal CART with orthostatic hypotension (>20/10 mmHg drop) identifies severe or advanced CAN.[630 (Level III)]
  - › Precautions prior to testing:[630 (Level III)]
    - optimise plasma glucose, and
    - avoid caffeine intake, smoking, or alcohol for at least 2 hours prior, and
    - avoid performing test within 2 hours after a main meal or prandial insulin injection.
  - › Use age-appropriate CART reference values when available.
- Diagnosis of gastroparesis
  - › By:[631 (Level III)]
    - a combination of symptoms (Refer Table 5-5),
    - demonstration of delayed gastric emptying time; and
    - exclusion of gastric outlet obstruction or ulceration.
  - › The gold-standard test to diagnose gastroparesis is gastric emptying scintigraphy.

B. Management

- Intensive control of modifiable CV risk factors have been shown to reduce the progression and development of CAN among patients with T2DM.[632 (Level I)]
- Avoid/minimise drugs that cause orthostatic hypotension.
  - › Midodrine has been approved as medical therapy for orthostatic hypotension.[6 (Level III)]
  - › Other recommended interventions include acute water ingestion for short-term relief, physical counter-pressure manoeuvres, compression garments, fludrocortisone, and increasing salt and water intake.[633 (Level III)]
- Exercise programs and multifactorial interventions for fall prevention has been shown to reduce the risk of falls in older people at moderate and high risk.[634 (Level III)]
  - › Consider referral to centres specialising in fall prevention (if available).

- Small frequent meals with low fat and fibre content are recommended in gastroparesis.[631,635 (Level III)]
- Prokinetic agents such as erythromycin aids in relieving gastroparetic symptoms but may be limited by tachyphylaxis.[636 (Level III)]
- Short-term metoclopramide may be used in severe cases.[6 (Level III)]
  - Long-term use of metoclopramide may be complicated by neuromuscular complications, e.g. tardive dyskinesia and extrapyramidal side-effects.[637]
  - Alternatively, domperidone acts similarly to metoclopramide, but with less neurological side-effects due to reduced penetration across the blood-brain barrier.[638 (Level III)]

Diabetic amyotrophy

- Diabetic amyotrophy, also known as proximal diabetic neuropathy, diabetic lumbosacral radiculoplexus neuropathy, or Bruns-Garland syndrome is an uncommon subtype of diabetic neuropathy affecting about 0.8% to 1% of people with diabetes.[639 (Level II-2) 640 (Level III)]
- It Is characterised by weakness and areflexia of asymmetric onset, pain on the affected site and marked weight loss.[641 (Level III)]

A. Diagnosis

- Is made by excluding nerve root compression with MRI.
- Supported by the presence of small amplitude sensory nerve action potential from nerve conduction studies, and fibrillation potentials and long duration high amplitude motor unit action potential from electromyogram.[641 (Level III)]

B. Management

- Treatment of pain due to diabetic amyotrophy follows similar recommendation for treatment for pain due to DSPN.[597 (Level III)]
- Data on the effect of glycaemic control on diabetic amyotrophy Is lacking. However, given the known benefits on preventing neuropathy and other diabetic complications, glucose control should be optimized.[641,642 (Level III)]
- Diabetic amyotrophy progresses over months, and eventually stabilises and improves.[643 (Level II-2)]

Recommendations: Neuropathy

1. Assessment for peripheral neuropathy should be performed at diagnosis and annually.	*Grade C*
2. Intensive lifestyle intervention has been shown to reduce the risk of diabetic peripheral neuropathy in people with prediabetes and T2DM.	*Grade B*
3. Tight control of plasma glucose and CV risk factors have been shown to reduce the progression and development of autonomic neuropathy.	*Grade B*
4. Treatment for pain due to DSPN include voltage-gated calcium channel α2-δ ligand (pregabalin, gabapentin), serotonin-norepinephrine reuptake inhibitor (duloxetine), or tricyclic antidepressants. Switching to another class of medication or combination therapy may be required if patients have poor response to the initial treatment.	*Grade B*
5. Refer patients to specialised pain centres if they require long-term opioid treatment.	*Grade C*

5.4 Cardiovascular disease

A. Coronary heart disease

SUMMARY OF UPDATES

- In addition to the importance of managing hyperglycaemia, management of the other traditional concomitant CV risk factors; i.e. BP and LDL-C remain important - with BP targets of 130-139/70-79 mmHg and LDL-C according to CV risk category, with proven clinically meaningful CV risk reduction.
- Recent CVOTs have proven that certain GLDs (GLP1-RAs and SGLT2-i) are also cardioprotective, beyond their glucose-lowering effects. These CV benefits are seen irrespective of HbA_{1c} level achieved. Paradigm shifts in management algorithm recommendations are emerging.
- There is an emerging role of SGLT2-i to reduce heart failure hospitalisations in high risk ASCVD patients.
- However, if these newer medications are not available, achieving HbA_{1c} safely, remains an important target.

- T2DM is associated with increased risk of coronary heart disease (CHD), manifesting as angina, MI, CCF and sudden death. In addition, T2DM may lead to diabetic cardiomyopathy. CHD accounts for up to 2/3rd of deaths associated with T2DM.[6 (Level III) 644 (Level II-2)]
- In the 2015-2016 acute coronary syndrome registry (National Cardiovascular Disease Database – NCVD-ACS registry), 44.7% of patients had T2DM as a CV risk. This was the 2nd most common CV risk factor, after hypertension at 63.3% (Available online at *http://www.acrm.org.my/ncvd/reports_annualReports.php*)[4 (Level II-3)]
- The increased risk of CHD in patients with T2DM is only partially 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.[645,646 (Level II-1)]

- 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.[647 (Level II-2)] Cardio-metabolic risks associated with T2DM and CHD in T2DM should be managed aggressively.[647,648 (Level II-2)]
- CHD in T2DM is characterised by its early onset,[649 (Level II-2)] extensive disease at the time of diagnosis, and higher morbidity and mortality after MI.[650,651 (Level II-2)]
- Angiographic findings in diabetes are more diffuse, involving multiple coronary arteries including small and distal vessels.[652 (Level II-2) 653,654 (Level I)]
- There is a strong and continuous association between proteinuria and future risk of CHD.[655 (Level I)]
- Heart failure hospitalisation incidence in people with T2DM (even after adjusting for confounders, e.g. age and sex) has been found to be 2-fold higher, compared to those without diabetes.[656-658 (Level II-2)]. Predictors of heart failure development were younger age and higher BMI.[658 (Level II-2)]
  - Poor glycaemic control is also associated with increased risk of HF; every 1% increase in HbA_{1c} is associated with an 8% increased risk of heart failure (95% CI 5%,12%).[659 (Level II-2)]
  - Approximately 40% of hospitalised heart failure patients with low ejection fraction have T2DM. Post discharge, T2DM is associated with worse prognosis, increased risk for combined CV mortality and heart failure-related re-hospitalisation.[660 (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 GI symptoms associated with exertion.[661 (Level II-1)]
- In asymptomatic patients, routine screening for coronary artery disease is not recommended because it does not improve outcome as long as they are receiving intensive medical therapy for optimal CV risk factor control.[662 (Level I)]
  - Risk calculators: There is uncertainty whether current strategies for providing CVD risk scores affect CVD events. The identified studies have multiple study limitations and substantial heterogeneity in interventions, outcomes and analyses making interpretation of results difficult.[663 (Level I)]
  - New models for implementing and evaluation CVD risk scores in adequately powered studies are needed to define the role of applying CVD risk scores in primary CVD prevention.

- Screening for presence of CHD should be done for:
  - T2DM patients with peripheral or cerebrovascular disease;[647,648 (Level I)] and
  - T2DM patients with presence of proteinuria and DKD.[655 (Level I)]
- Resting electrocardiogram (ECG) is indicated for T2DM patients:
  - with hypertension; or
  - if CVD is suspected.[664 (Level II-2)]

Recommendations: Screening for CVD

1. In asymptomatic patients, routine screening for coronary artery disease is not recommended. Routine screening does not improve outcomes as long as ASCVD risk factors are treated to target.	*Grade A*
2. In asymptomatic patients whose CV risk factors are not to target.	*Grade A*
3. A resting ECG is indicated in patients with T2DM and hypertension, or if CVD is suspected.	*Grade B*

Management

I. General management

- Lifestyle modification, weight management and increased physical activity are important measures.[95,665-667 (Level I)]
  - Reduced caloric intake to lower excessive body weight and regular moderate-to-vigorous physical activity of ≥150 minutes/week is beneficial in improving CV risk factors, glycaemic control and inducing remission of T2DM. (Refer Section 3.5)
  - Mortality and CV event reduction with lifestyle intervention alone has not been demonstrated in RCTs.
- Smoking cessation is strongly recommended and a high priority.[668 (Level I)]
  - Smoking increases the risk of CVD and premature death.

II. Glycaemic control

- Intensive glycaemic control has more beneficial CV effects when achieved early and maintained throughout the course of T2DM management.[310,376,377 (Level I)]

- For management strategies of hyperglycaemia in patients admitted with acute coronary syndrome/unstable angina/heart failure, refer to Section 6.1 (management in acute illness).
- In patients with T2DM with stable heart failure, metformin may be continued if estimated glomerular filtration rate remains >30 mL/min/1.73 m^2.[669 (Level II)]
- TZDs should be avoided in patients with pre-existing heart failure due to increased risk of fluid retention.[303 (Level I)]
- DPP4-i have demonstrated CV safety (TECOS, CARMELINA SAVOR-TIMI).[160,191-193 (Level I)]
  - › However, saxagliptin should be avoided in patients with pre-existing heart failure[6 (Level III)] as it has been shown to be associated with increased risk of hospitalisation for heart failure.[193 (Level I)]
- SGLT2-i/GLP1-RA have been shown to demonstrate CV benefit in those with ASCVD or who are at high CV risk irrespective of HbA_{1c} achieved.[201,202,248,259,670-672 (Level I)]
- In addition, SGLT2-i in T2DM with ASCVD or high risk for ASCVD or DKD have been confirmed to significantly reduce hospitalisation for heart failure.[201,203,673-676 (Level I)] Most of the patients in these trials did not have heart failure at baseline (ranging from 10.0%-14.4%).
  - › A meta-analysis of two dedicated heart failure trials,[950 (Level I)] DAPA-HF[206 (Level I)] and EMPEROR-Reduced,[951 (Level I)] that recruited patients with HFrEF (42-50% with known T2DM) showed:
    - Over a median of 16.0-18.2 months, there was a significant reduction in risk of CV death or heart failure (HR 0.75, 95% CI: 0.68-0.84, p<0.0001) vs. placebo.[950 (Level I)]
    - There was also significant reduction in first hospitalisation for heart failure (HR 0.69, 95% CI: 0.62-0.78, P<0.0001) vs. placebo.[950 (Level I)]
    - These significant benefits were seen in both patients with T2DM as well as those without (Refer to Section 3.6-SGLT2-i).[206,950,951 (Level I)]
  - › These heart failure benefits are found irrespective of glucose-lowering and also in non-diabetic subjects,[206,950 (Level I)]
  - › SGLT2-i has been given a specific indication for use to reduce hospitalisation for heart failure in adults with T2DM with ASCVD or multiple CV risk (use SGLT2-i that has label indication for heart failure prevention).
- Less rigorous glycaemic targets may be appropriate for elderly patients and those with severe co-morbidities or advanced CVD.[310 (Level III)]

III. BP control (Refer to Section 3.9.1)

- BP control to target of 130-139/70-79 mmHg with coronary artery disease (existing ASCVD or 10-year ASCVD of ≥15%) if it can be safely achieved.[361-366 (Level I)]

- In patients with known ASCVD, consider ACE inhibitor[368,369 (Level I)] or ARB therapy if ACE inhibitor intolerant[370 (Level I)] to reduce the risk of CV events.

IV. Lipid control (Refer to Section 3.9.2)

V. Antiplatelet therapy

- There is strong evidence that aspirin is effective for secondary prevention of cardiovascular events.[677,678 (Level I)]
- The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study showed that daily low-dose aspirin (81 or 100 mg daily) taken for >4 years in asymptomatic people with T2DM failed to show a significant effect on a broad composite of CVD endpoints. However, the risk of fatal coronary or cerebrovascular events was significantly decreased in the aspirin group in those >65 years old.[549 (Level I)]
- A recent large primary prevention trial (ASCEND trial) showed reduction in CV events but with an increased rate of GI haemorrhage.[679]
  - 2 other studies showed no benefit in primary prevention.[680,681]
  - In general, those with low risk (<50 year of age with no major risk for ASCVD) aspirin is not recommended as primary prevention.
- However, in those who are at increased CV risk, aspirin therapy may be considered after a discussion with the patient on the benefits vs. increased risk of bleeding.[549,678,679,682,683 (Level I)]
- For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) may be used.[677 (Level I)]

VI. Revascularisation

- In T2DM patients with NSTEMI, early invasive revascularisation (where possible), will result in similar or greater reduction in death and MI compared to the overall population.[684 (Level I)]
- T2DM should be considered as a distinct disease entity that is critical for the selection of myocardial revascularisation strategies in multi vessel disease.
  - Current evidence indicates that in stable patients with coronary anatomy suitable for both procedures and low predicted surgical mortality, CABG is superior to PCI in reducing the composite risk of death, MI, or stroke, as well as death.[685-687 (Level I)]
- Presence of diabetic retinopathy is not a contraindication for thrombolytic therapy.[688 (Level II-1)]

Recommendations: Management of CVD

1. Lifestyle measures remain important, including: a. attainment of appropriate weight, increased physical activity; and b. smoking cessation.	*Grade A*
2. Multi-factorial management to achieve glycaemic, BP and lipid targets to reduce CV events.	*Grade A*
3. Aspirin should be used for secondary prevention in T2DM patients. For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used.	*Grade A*
4. Primary prevention of ASCVD with low dose aspirin (100 mg) is only recommended in patients at increased cardiovascular risk after discussion with the patient on benefits vs. risk of bleeding.	*Grade A*
5. In patients with T2DM with established atherosclerotic cardiovascular disease, consider adding SGLT2-i/ GLP1-RA with demonstrated CV benefit as part of the glucose lowering regimen.	*Grade A*
6. Among patients with ASCVD with pre-existing or at high risk of heart failure (HFrEF) SGLT2-i should be considered, even if HbA_{1c} is at target.	*Grade A*
7. In patients with T2DM and multi vessel coronary artery disease or complex left anterior descending coronary artery disease, and suitable coronary anatomy for revascularization, CABG is superior to PCI.	*Grade A*

B. Cerebrovascular disease (Stroke)

SUMMARY OF UPDATES

- 3-point MACE outcomes in the recent CVOTs incorporate non-fatal stroke as part of the composite CV outcome.
- Recent GLP1-RA trials (SUSTAIN-6 and REWIND) have found positive 3-point MACE outcome, largely driven by reduction in non-fatal stroke. These interesting findings may need to be confirmed in dedicated cerebrovascular event trials.

- Hyperglycaemia which is present in 40% of patients with stroke on admission, is strongly predictive of poor clinical outcomes and high mortality.[689 (Level 11-2)]
- The Asia-Pacific Cohort Studies Collaboration (APCSC) found that the HR for ischaemic stroke was 2.64 (95% CI 1.78,3.92); and the age, sex adjusted HR for death from cerebrovascular disease was 2.02 (95% CI 1.57,2.59) in individuals with T2DM, compared to non-T2DM. The ratios were the same in the Asian and Australasian subgroups.[690 (Level II-2)] The risk of stroke is higher in women than in men.[647,648 (Level II-2)]
- There is no recommendation for intensive IV or SC insulin in these patients as there was no improvement in functional outcomes at 90 days.[691 (Level I)]
- Thiazolidinediones (TZDs), PROACTIVE cardiovascular outcome trial (CVOT) showed positive outcomes for 3-point MACE of which the most significant was reduction of 47% of recurrent stroke.[692 (Level 1)] However, side-effects of TZDs of weight gain, increased risk of CHF and osteoporotic fracture render the benefit-risk ratio unfavourable.
- GLP1-RA CVOTs have shown positive 3-point MACE outcomes largely driven by significant reduction of non-fatal stroke (39% risk reduction in SUSTAIN-6 and 24% risk reduction in REWIND).[248,259 (Level I)]

Recommendations: Stroke

1. Patients with ischaemic stroke should be managed similarly as patients with established ASCVD.	*Grade B*

C. Peripheral arterial disease (PAD)

SUMMARY OF UPDATES

- Absent peripheral pulses are independent predictors of major vascular outcomes in patients with T2DM These clinical indicators can be used to improve risk stratification for patients with T2DM.
- Presence of critical limb ischaemia features (e.g. rest pain with ulcers or tissue loss) identifies a high-risk individual for amputation and/or mortality. Urgent referral to specialist care is indicated.

- People with T2DM have a three-fold increased risk of developing peripheral arterial disease (PAD), which mainly affects the infra-popliteal arteries.[693 (Level III)]
- The diagnosis of PAD in T2DM is often delayed due to the presence of concomitant neuropathy which results in the lack of typical PAD symptoms.[43,694 (Level III)]
- Absence of peripheral pulses has been shown to be an independent predictor of risk for major CV outcomes, heart failure and nephropathy.[695 (Level II-1)]
- Risk factors for PAD in T2DM include:[696,697 (Level II-2)]
  - older age
  - higher HbA_{1c}
  - elevated SBP
  - low HDL-C levels
  - previous CVD
  - smoking

Assessment

- All patients with T2DM undergoing annual screening for peripheral neuropathy should also be assessed for peripheral vascular disease, with appropriate history taking and palpation of the peripheral pulses (femoral, popliteal, posterior tibial and dorsalis pedis artery).[693,694,698 (Level III)]
- If PAD is suspected from the initial screening, several non-invasive bedside tests can be done for further evaluation (Table 5-6).[43,694,698,699 (Level III)]
  - Ankle brachial index (ABI) is used widely due to feasibility.
  - Toe brachial index (TBI) is useful in the presence of medial calcinosis.

Table 5-6: Non-invasive bedside tests for evaluation of PAD.

Test	Result	Implication	Recommended alternative action
Ankle brachial index (ABI)	<0.90	Diagnostic for PAD	
	0.90-1.3*	PAD less likely	
	>1.3	May be due to medial calcinosis	Other tests e.g. TBI or CWD recommended
Toe brachial index (TBI)	<0.70	Diagnostic for PAD	
	≥0.75	PAD less likely	
Continuous wave Doppler of ankle arteries (CWD)	Triphasic pedal Doppler waveforms	PAD less likely	

**Note: ABI values may be falsely elevated in diabetes due to vessel stiffening/calcification.*

- In patients with T2DM and a foot ulcer, clinical examination alone may not exclude PAD hence combined modality testing of CWD and ABI or TBI is recommended.[694 (Level III)]
- Patients with features of critical limb ischaemia (rest pain with ulcers or tissue loss due to PAD) are at high risk of amputation and mortality and should be referred urgently for specialist care.[700,701 (Level III)]

Management

- Principles of PAD management in T2DM:[699 (Level III)]
  - › Reducing CV risk factors and treating concomitant disorders.[43,694 (Level III)]
    - Smoking cessation and lifestyle modification.
    - Statins for secondary prevention of CV events; aim for LDL-C <1.4mmol/L or LDL-C reduction of at least 50% from baseline.
    - Adequate blood pressure and glycaemic control.
    - Anti-thrombotic therapy.[43,699 (Level III)]
    - Single anti-platelet therapy (SAPT) is recommended only in symptomatic PAD or after revascularization.
    - For those requiring SAPT, clopidogrel may be preferred over aspirin.[677 (Level I)]
    - Double anti-platelet therapy (DAPT) is used only for a limited period after certain revascularization procedures.
    - Combination therapy of low-dose rivaroxaban (2.5 mg bd) and aspirin (100 mg od) can be considered in patients with chronic symptomatic PAD and T2DM who do not have a high risk of bleeding.

» In the COMPASS trial PAD sub analysis, the aspirin-rivaroxaban combination significantly reduced composite endpoint of stroke, MI or CV death, major adverse limb events and amputations. However, a significant increase in major bleeding risk, particularly GI bleeding, was observed.[702 (Level I)]

- Improving peripheral circulation in symptomatic patients.[43,694,699 (Level III)]
  - › Those with symptoms of PAD and diabetic foot ulcer/infection must be assessed and treated urgently as they are at a high risk for major limb amputation.
  - › Revascularization must be attempted when possible and amputation only considered when revascularization options fail.
  - › Consider revascularization in a patient with PAD and a diabetic foot ulcer that is not healing despite 4-6 weeks of optimal management.
  - › Patients with intermittent claudication can improve their walking distance by doing regular exercise training programmes. However, those with severe/disabling claudication may require revascularization.

Recommendations: Peripheral Arterial Disease

1. Patients with suspected PAD from initial screening are recommended to be further evaluated with bedside tests such as ABI, TBI or CWD.	*Grade B*
2. It is recommended that patients with PAD receive appropriate treatment to achieve adequate control of their CV risk factors.	*Grade B*
3. Antiplatelet therapy is indicated for secondary prevention of CV events in patients with symptomatic PAD.	*Grade B*
4. Critical limb ischaemia warrants prompt referral and multidisciplinary management.	*Grade C*

5.5 Diabetic foot

SUMMARY OF UPDATES

- Screening for peripheral neuropathy with loss of protective sensation (LOPS) and peripheral arterial disease (PAD) should be done at diagnosis and repeated at least annually.
- High risk feet (history of ulcers or amputations, foot deformities, LOPS, PAD) will need more frequent detailed foot assessment.

- The prevalence of diabetic foot ulcer is 15% over the course of the disease[703] (Level II-2) while the prevalence of lower limb amputation is 4.3%[704] (Level III) and remains a major cause of morbidity and mortality.
- Peripheral neuropathy which is asymptomatic in up to 50%[704] (Level III) of patients, predisposes to ulcerations and vasculopathy further retards the healing process.

Risk factors for foot ulcers and amputation

- Risk factors include:[6,705] (Level III)
  - previous amputation,
  - history of foot ulcer, pre-ulcerative callous or corn, and foot deformity,
  - peripheral neuropathy with loss of protective sensation (LOPS),
  - peripheral arterial disease (PAD),
  - visual impairment,
  - DKD – especially patients on dialysis,
  - poor glycaemic control, and
  - cigarette smoking.

Assessment of diabetic foot ulcers

- All patients with T2DM should be assessed for risk of diabetic foot ulcers with proper history taking and comprehensive foot evaluation (Refer the Malaysian CPG for Management of Diabetic Foot [2nd edition] available at *http://www.moh.gov.my/moh/resources/Penerbitan/CPG/Orthopaedics/Draft%20CPG%20Diabetic%20Foot.pdf*)[6,698] (Level III)

- Screening for peripheral neuropathy with LOPS and PAD should be done at diagnosis and repeated at least annually.[694,698 (Level III)] For peripheral neuropathy with LOPS, refer to Section 5.3.
  - › For PAD assessment is by palpation of foot pulses. Ankle brachial index testing should be performed.
- Those at high risk (history of ulcers or amputations, foot deformities, LOPS, PAD) will need more frequent detailed foot assessment.[706 (Level III)]

Prevention

- All patients with T2DM should receive foot care education at least annually, and more frequently in those with high risk foot conditions.[694,698 (Level III)]
- Relevant patient education such as:[6,694,698 (Level III)]
  - › proper care of feet including nail and skin care,
  - › daily visual inspection of feet with a mirror, in those with LOPS,
  - › check for presence of foreign or penetrating objects before putting on footwear,
  - › advise not to walk barefoot outdoors or indoors,
  - › selection of appropriate footwear according to foot risk, including certain prescribed footwear for high risk patients; and
  - › seek early treatment in presence of active diabetic foot problems (e.g. ulceration, infection, gangrene or limb ischaemia).

Management

- Patients with active diabetic foot problems (ulceration, infection, gangrene, critical limb ischaemia, acute Charcot neuroarthropathy) should be referred urgently and seen within 24 hours in secondary/tertiary care, and preferably managed by a multidisciplinary foot care team.[698 (Level III)]
- Trauma induced ulcers with no other risk factors will require the standard wound care and close follow-up until full recovery.
- Antibiotics should be used as an adjunct to surgical debridement for diabetic foot ulcers with local or systemic infection but should not be used to prevent infection.[694,698 (Level III)]
- Appropriate analgesia should be given for adequate pain relief in those with painful neuropathy.[698 (Level III)]

Recommendations: Diabetic foot

1. All patients with T2DM are recommended to have at least annual comprehensive foot assessment to identify individuals with risk factors, as well as receive foot care education to avoid ulcers and amputations.	*Grade B*
2. Active diabetic foot ulceration, infection, gangrene, critical limb ischaemia require urgent referral and appropriate management.	*Grade C*
3. A multidisciplinary approach is recommended for patients with foot ulcers and high-risk feet.	*Grade B*

5.6 Sexual dysfunction

SUMMARY OF UPDATES

- Erectile dysfunction is common in T2DM men. It has been reported to be a marker for potential CVD. Screening for CHD in T2DM men with ED is recommended.
- Hypogonadism also occurs more frequently in T2DM men and should be excluded.
- Testosterone therapy improves response to PDE-5 inhibitors.

5.6.1 Erectile dysfunction

- 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.[707,708 (Level II-3)]
- The prevalence of ED among diabetic men varies from 35% to 45%.[709-717 (Level II-3)]
  - › ED is three times more common in men with T2DM and its annual, age-adjusted incidence is doubled compared to men without T2DM.[718,719 (Level II-1)]
  - › Compared to men without T2DM, it occurs 10-15 years earlier and is less responsive to treatment.[719-721 (Level II-3)]

- ED has been reported to be a marker for potential CVD, with significant association with all-cause mortality and CV events.[722-725] (Level II-2)
- Risk factors of ED[710-712,721,726-729] (Level II-2)
  - › Advancing age, duration of T2DM, poor glycaemic control, presence of diabetic microvascular complications, CV disease, hypertension, hyperlipidaemia, sedentary lifestyle, cigarette smoking and androgen-deficiency/hypogonadism.
- Rates of hypogonadism are higher in men with T2DM compared to the general population.
  - › Prevalence of 30%-40% hypogonadotrophic hypogonadism has been reported in men with T2DM.[730,731] (Level II-2)
  - › Symptoms and signs suggestive of hypogonadism are reduced libido, absence of early morning erection and testicular atrophy.

Screening and diagnosis

- All adult men with T2DM should be regularly screened for ED. Many patients do not voluntarily offer the history.[732]
- All patients with T2DM and ED should be screened for CHD.
- Hypogonadism should be excluded in men with T2DM and ED.
  - › Early morning blood for total testosterone (taken before 11.00 am) should be performed.[733] (Level III)
- Screening can be done using the 5-item version of the International Index of Erectile Function (IIEF) questionnaire (Refer Appendix 10).[734,735] (Level I)

Management

- No RCTs have shown that improving glycaemic control directly prevents or improves ED.
- However, indirect evidence derived from the UKPDS[541] and ACCORD[610] showed that early intensive glucose control reduced the incidence of neuropathy, which is a major contributing factor for ED.
- Optimisation of glycaemic control, management of other co-morbidities and lifestyle modifications should be encouraged.[(Level III)]
- Psychosexual counselling is recommended in functional ED.

- Where possible, avoid medications that may cause or worsen ED such as:
  - beta blockers, alpha blockers, calcium channel blockers, diuretics,
  - tricyclic antidepressants, SSRIs, lithium, neuroleptics; and
  - anticonvulsants.
- Phosphodiesterase-5 (PDE-5) inhibitors e.g. sildenafil, tadalafil and vardenafil should be offered as first-line therapy.[736-740 (Level I)]
  - There is evidence that scheduled daily therapy is effective in the population with T2DM and ED[741 (Level I) 742 (Level II-1)] and may improve efficacy with lower rates of side effects.
  - PDE-5 inhibitors are contraindicated in unstable angina, poor exercise tolerance or concomitant nitrate medication.
  - Referral to a urologist may be necessary for those not responding to PDE-5 inhibitors or in whom PDE-5 inhibitors is contraindicated.[743 (Level III)]
- Other therapies include intracavernosal injections, intraurethral alprostadil, vacuum devices with constricting band and surgery.
- Testosterone therapy should only be offered to those who are proven to have hypogonadism and are symptomatic.[744 (Level I) 745 (Level II-2)]
  - Testosterone therapy improves the efficacy of PDE-5 inhibitors.[746 (Level II-1) 747 (Level II-2)]
  - Several non-randomised, observational studies have produced conflicting results with regards to cardiac risk vs. benefit from testosterone replacement.[748 (Level I) 749,750 (Level II-2)]

Testosterone replacement therapy for ED

1. Biochemical confirmation of hypogonadism
2. Testosterone (parenteral/oral/transdermal)
3. PDE-5 inhibitor

Recommendations: Erectile dysfunction

1. All adult men with diabetes should be screened for ED.	*Grade C*
2. Optimisation of glycaemic control and other risk factors should be encouraged.	*Grade C*
3. PDE-5 inhibitor should be offered as first-line therapy if there are no contraindications.	*Grade A*
4. Testosterone therapy should be considered in symptomatic hypogonadal men as it improves response to PDE-5 inhibitor therapy.	*Grade A*
5. Referral to a urologist 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*

5.6.2 Female sexual dysfunction

- Female sexual dysfunction (FSD) is defined as persistent or recurring decrease in sexual arousal, dyspareunia and difficulty or inability to achieve an orgasm that leads to personal distress and relationship difficulties.[751 (Level III)]
  - › It consists of female sexual interest/arousal disorder, orgasmic disorder and genito-pelvic pain/penetration disorder.[752 (Level III)]
  - › Most women experience a combination of these disorders.
- FSD is estimated to occur in 24-75% of women with T2DM.[753-761 (Level III)]
- Risk factors:
  - › Age, duration of diabetes, poor glycaemic control, menopause, micro- and macro-vascular T2DM complications, and psychological factors (depression and anxiety disorder).[754-756,759,761-763 (Level II-2)]

Screening and diagnosis

- All women with T2DM should be asked about sexual dysfunction.
- Brief sexual symptom checklist can be used as initial screening.
- The patient's medical, surgical, social and psychiatric history should also be obtained.

- Diagnosis of FSD can be established by using FSFI questionnaire that consists of 19 questions covering all domains of sexual dysfunction[764 (Level III)] available at *www.fsfiquestionnaire.com*.
- Physical examination should include assessment of thyroid status or for presence of galactorrhoea.
- Gynaecological examination should be performed if indicated.
- Oestrogen deficiency is usually detected by history and examination.
- Investigations[764 (Level III)]
  - › General
    - Haemoglobin
    - To rule out metabolic dysfunction
  - › Endocrine
    - Thyroid
    - Prolactin and gonadotropins
    - To rule out pituitary dysfunction
- Routine laboratory testing for testosterone and dehydroepiandrosterone (DHEAs) levels are not recommended.[764 (Level III)]

Management

- Emphasis should be made to treat psychosocial disorders and relationship disharmony.
- Optimisation of glycaemic control should be encouraged.
- Where possible, avoid drugs that may affect sexual function:
  - › beta blockers, alpha blockers, calcium channel blockers, diuretics,
  - › tricyclic antidepressants, SSRIs, lithium, neuroleptics,
  - › anticonvulsants,
  - › oral contraceptive pills.
- In postmenopausal women, tibolone has been associated with significant increases in sexual desire and arousal provided there are no contraindications.[765 (Level I)]
- Topical lubricants, vaginal moisturisers and local oestrogen application aid with vaginal dryness and dyspareunia.
- Androgen, DHEAs and PDE5 inhibitor are not recommended.[766,767 (Level III)]

Recommendations: Female sexual dysfunction

1. FSD is common and should be screened and managed where appropriate.	*Grade C*

5.7 Mental health issues in T2DM

SUMMARY OF UPDATES

- Diabetes distress/depression is common and increasingly recognised as a barrier to patients' ability to cope and self-manage their diabetes.
- Psychological and social factors need to be assessed as an integral part of management.
- Referral to a Mental Health specialist may be indicated in specific circumstances.

- Psychological comorbidity, such as depression and/or diabetes-specific emotional distress (diabetes distress), is widespread in people with T2DM with an overall prevalence of 36% for diabetes distress and 15% for depression.[768,769 (Level II-2)]
- In a study involving 2508 patients with T2DM from 12 health clinics in Malaysia, 11.5% were found to have depression.[770 (Level II-2)]
- Psychological and social factors are important influences on the ability of patients to cope with the daily demand of diabetes care and self-management.
- Patients with depression and diabetic distress are more likely to have poorer health outcomes including uncontrolled blood sugars,[771 (Level III)] complications from diabetes, reduced quality of life and higher rates of all-cause mortality.[772 (Level I)]
- It is pertinent to address mental status of T2DM:
  - at the time of diagnosis
  - at diagnosis of complications
  - when there is loss of glycaemic control/lack of treatment compliance
  - at time of treatment intensification.

- Symptoms to look for may include prolonged period of moodiness with any or all of the following:
  - appetite changes,
  - loss of interest in daily activities,
  - feeling of despair,
  - inappropriate sense of guilt,
  - sleep disturbance,
  - weight loss,
  - suicidal thoughts.
- Indications for referral to a mental health specialist may include:
  - depression with the possibility of self-harm,
  - debilitating anxiety (alone or with depression),
  - indications of an eating disorder,
  - cognitive functioning that significantly impairs judgment.
- Behavioural treatment interventions which include cognitive behavioural therapy and exercise as shown in Program ACTIVE II has demonstrated clinically meaningful improvements in depression outcomes in adults with T2DM and major depressive disorder.[773 (Level I)]
- It is important to acknowledge that mental health well-being is a very important part of diabetes management.[774,775 (Level III)]

Recommendations: Mental health issues in T2DM

1. Diabetes distress/depression is common. 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*

5.8 Periodontal disease in T2DM

SUMMARY OF UPDATES

- Oral health education should be provided to all patients with T2DM emphasizing the increased risk of periodontal disease in T2DM. This should include:
  - the bi-directional relationship of periodontal disease and T2DM
  - adverse effects on HbA_{1c} control due to untreated periodontal disease
  - successful management of periodontal disease will improve metabolic parameters
- There is a direct relationship between periodontitis and cardio-renal complications of T2DM. T2DM patients with periodontitis have been found to have an increased CV mortality and morbidity, and also increased mortality in patients with DKD.

- Periodontal disease is a chronic inflammatory disease, comprising two main categories:
  - gingivitis; and
  - periodontitis which involves destruction of the tooth supporting structures such as the alveolar bone, periodontal ligament and cementum. If left untreated it causes tooth loss.[776] (Level III)
- Signs and symptoms include:
  - bleeding gums during brushing or eating,
  - loose teeth, spacing or spreading of the teeth,
  - oral malodour; and/or
  - abscesses in the gums or gingival suppuration.
- Severe periodontitis is a major cause of tooth loss, nutritional compromise, altered speech, low self-esteem and a poorer overall quality of life.[67] (Level II-2)
- The bi-directional effects of periodontitis and T2DM
  - Individuals with T2DM have been reported to be approximately twice as likely to have more severe periodontal attachment loss than those without T2DM, after controlling for other variables.[65,777-779] (Level II-2)

- › Clinical studies have shown that elevated levels of pro-inflammatory mediators within the periodontal tissues of people with poorly controlled T2DM play a role in increased periodontal destruction[70 (Level III)] as well as contribute to insulin resistance and worsening glycaemic control.[780 (Level III)]
- › Severe periodontitis has been associated with increased HbA_{1c} levels.[66 (Level II-2)]
  - The magnitude of increase in HbA_{1c} attributed to periodontitis in T2DM was 0.29% (95% CI 0.20,0.27).[66 (Level II-2) 70 (Level III) 781 (Level I)]
  - Subjects with severe periodontitis are at an increased risk of developing (incident) T2DM (adjusted HR 1.19-1.33).[66 (Level II-2)]

- There is a direct relationship between the severity of periodontitis and cardio-renal complications of T2DM.[66,782 (Level II-2)]
  - › The comorbid presence of periodontitis and T2DM in patients with DKD is reported to elevate the 10-year all-cause mortality risk by 23% and CV mortality risk by 16%.[783,70 (Level III)]
  - › CV complications (CV mortality, CHD or cerebrovascular events, and subclinical heart disease) have also been significantly associated with the comorbid presence of T2DM and periodontitis (OR 2.2-2.6; 95%CI 1.4-4.2).[66,784 (Level II-2)]

Management

- Current evidence indicates that in people with T2DM, periodontal therapy accompanied by effective self-care is both safe and effective. Clinical periodontal parameters improve following standard non-surgical therapy even in people with poorly controlled T2DM.[70 (Level III) 785 (Level I)]

- Systematic reviews and meta-analyses have concluded that HbA_{1C} reductions ranges from 0.27% to 0.48% at 3-4 months following periodontal therapy.[781,785-787 (Level I)]

- The adjunctive use of antibiotics does not enhance HbA_{1C} reduction beyond scaling and root surface debridement alone among people with T2DM.[70 (Level III) 785 (Level I)]

- As evidence mounts supporting the link between T2DM and periodontitis, closer collaboration between physicians and oral health care professionals is warranted to improve glycaemic control.[70,788 (Level III) 69 (Level II-2)]

- Additionally, there is a need for healthcare providers to routinely refer these patients for oral healthcare as part of the holistic care for people with T2DM.[70 (Level III) 68,69 (Level II-2)]

Recommendations: Periodontal disease

1. Oral health education should be provided to all patients with T2DM emphasizing on the increased risk of periodontal disease in T2DM. **Successful management of periodontal disease will improve metabolic parameters.**	*Grade A*
2. Physicians/medical health professionals should investigate the presence of periodontal disease as an integral part of T2DM care visits. If present, prompt referral should be made to the dentist for periodontal examination.	*Grade C*
3. For all people with newly diagnosed diabetes, referral for a periodontal examination should occur as part of their management. Even if no periodontitis is diagnosed initially, annual periodontal review is recommended.	*Grade C*

SECTION 6

T2DM IN SPECIAL POPULATIONS

SUMMARY OF UPDATES

- Management of T2DM in acute illness, stress and surgery
  - › HbA_{1c} should be considered for inpatients with hyperglycaemia or known T2DM if it has not been done for the last 3 months.
  - › Insulin is the preferred pharmacological therapy for most hospitalised patients with T2DM or hyperglycaemia.
- T2DM in adolescents
  - › Studies note that T2DM in the young represent a more severe and rapidly progressive disorder than in adults, with a faster rate of β-cell failure. This recognition has therapeutic significance with regard to need for escalation of therapy.
  - › Although metformin and insulin are the mainstay of therapy for adolescents with T2DM, liraglutide (a GLP1-RA) therapy may be considered.
- T2DM in the elderly
  - › Plasma glucose and capillary plasma glucose should be used to monitor glycaemic control.
  - › Optimal nutrition and regular exercise are recommended to reduce frailty.
  - › Annual cognitive screening is recommended.
  - › Treatment de-escalation or discontinuation should be considered in patients with multiple co-morbidities and poor life expectancy.
- T2DM in Ramadan
  - › Risk categories have been modified into 3 main groups: very high, high and moderate/low risk.
  - › Recommendations for self-monitoring of plasma glucose particularly in insulin treated T2DM individuals.
  - › SGLT2-i are generally safe in patients without advanced renal disease.
  - › GLP1-RA are safe and effective in reducing weight and maintaining HbA_{1c}.

6.1 Management of T2DM in acute illness, stress and surgery

- Hyperglycaemia in acute illness may reflect previously known or undiagnosed T2DM.
  - › Acute illness results in a number of physiological changes (e.g. increase in circulating concentrations of stress hormones) or therapeutic interventions (e.g. glucocorticoid use) that can exacerbate hyperglycaemia.[789 (Level III)]
- Hyperglycaemia in turn, causes physiological changes that exacerbate the acute illness, such as decreased immune function and increased oxidative stress. This leads to a vicious cycle of worsening illness and poor glycaemic control.[789 (Level III)]
- Both, hyper- and hypoglycaemia among inpatients are associated with adverse outcomes, including death.[790-792 (Level I) 793 (Level II-3)]
  - › Inpatient hyperglycaemia is associated with a mortality rate of 11.2%.[794 (Level II-2)]
- A dedicated inpatient diabetes service applying well-developed standards and careful transition to prearranged outpatient management is important to improve patient outcomes.[795,796 (Level II-2)]

Inpatient hyperglycaemia in acute illness

- Hyperglycaemia in hospitalised patients can occur in those with:
  - › pre-existing T2DM; or
  - › no known history of T2DM.
- Inpatient hyperglycaemia is defined as any glucose value >7.8 mmol/L in patients with no previous history of T2DM.[797 (Level III)]
- HbA_{1c} should be considered for inpatients with hyperglycaemia or known T2DM if it has not been done for the last 3 months.
  - › Admission HbA_{1c} has been found to be a good predictor of glycaemic control and response to insulin treatment, and tailoring treatment on discharge.[798,799(Level II-2)]

Glycaemic control

A. In non-critically ill patients[790-793,800,801 (Level I)]

- Insulin is the preferred pharmacological therapy for most hospitalised patients with T2DM or hyperglycaemia.

- In non-critically ill patients with T2DM, scheduled insulin regimens are recommended to manage hyperglycaemia.
  - During admission, OGLDs should be stopped when there is:
    - poor oral intake,
    - acute kidney injury,
    - exposure to IV contrast dye (specifically for those on metformin),
    - increasing severity of illness (illness becomes critical); and/or
    - organ failure (e.g. renal failure, liver failure or heart failure).
  - Regimens using insulin analogues and human insulin result in similar glycaemic control in the hospital setting.[802 (Level I)]
  - However, stable patients without the above conditions or contraindications to medications used can have their home medications continued while in the hospital.[789,793,800 (Level II-2)]
- In non-critically ill hyperglycaemic patients (with/without known T2DM) who are
  - taking orally well, options include basal bolus regimen or oral therapies provided no contraindications.[791,792 (Level I)]
  - not taking orally well or kept nil by mouth, options include basal plus insulin regimen or variable rate intravenous insulin infusion.[791,792 (Level I)]
- The target plasma glucose of 7.8 mmol/L-10 mmol/L is recommended for majority of non-critically ill patients.[797 (Level III)]
- Avoid plasma glucose values ≤3.9 mmol/L; if present, the glucose-lowering therapy should be modified, unless the event is easily explained by other factors (e.g. a missed meal).[797 (Level III)]

B. In critically ill patients[803-812 (Level I)]

- Appropriate glycaemic targets for patients with in-patient hyperglycaemia who are critically ill (ICU setting) have not been firmly established.[803-812 (Level I)]
- Intensive insulin therapy (targeting plasma glucose of 4.5 mmol/L-6.0 mmol/L) has been associated with an increased risk of hypoglycaemia and mortality in the ICU setting compared to conventional glycaemic control (targeting plasma glucose of <10 mmol/L).[806 (Level II-1)]
- Therefore, it is recommended to maintain plasma glucose levels between 7.8 mmol-10 mmol/L in critically ill patients.
- Variable Rate Intravenous Insulin infusion (VRIII) protocols with proven efficacy and safety are recommended to minimise the risk of hypoglycaemia.[813,814 (Level III)]

C. In surgery[803,804,807-812,815-826 (Level I)]

- Acute hyperglycaemia during surgery increases postsurgical complications, morbidity and mortality.
- Tight glycaemic control to achieve normoglycaemia while avoiding hypoglycaemia is recommended.
- Plasma glucose target recommended is 6.0 mmol/L-10 mmol/L.[815,827,828 (Level II-2)]
- Strategies for glycaemic control[815 (Level II-2)]
  - › If plasma glucose is within target, current regimen may be continued provided there is no contraindication for the agent.
  - › If plasma glucose is above target, to consider SC insulin regimen or VRIII.
  - › During intra-operative period and/or fasting, stop OGLDs and convert to insulin i.e. basal plus insulin or VRIII.
  - › Once tolerating orally with stable plasma glucose, to resume previous pre-operative regimen.

Use of insulin

- The use of sliding scale insulin (SSI) in inpatient hospital setting is strongly discouraged.
- SSI protocols, which are extensively used, when compared to a basal-bolus regime have been shown to be associated with:
  - › increased glycaemic variability; and
  - › longer time to achieve glycaemic target.[792,829 (Level I)]

D. Special clinical situations

- Patients receiving enteral or parenteral feeding
  - › In patients receiving continuous enteral feeding, options include basal plus, basal bolus or VRIII.[830,831 (Level I)]
  - › In patients receiving parenteral feeding, options include basal plus, bolus insulin only or VRIII.[831,832 (Level I)]
- Patients receiving corticosteroid therapy
  - › All patients receiving glucocorticoids equivalent to Prednisolone of ≥5mg/day should have their plasma glucose monitored for 24-48 hours and insulin commenced if plasma glucose is persistently high.
  - › Choices of regimen include:[833,834 (Level I)]
    - basal bolus,
    - bolus (prandial) + NPH OM/BD
    - VRIII

- Patients on continuous SC insulin infusion (CSII)
  - In absence of contraindications, CSII can be continued during hospitalisation.
  - If patient is unable (mentally or physically) to manage CSII or there is presence of contraindications, it can be converted to basal bolus insulin regimen or VRIII according to the situation.[835,836 (Level III)]

Transition from hospital to home

- During recovery, education on diabetes care including treatment regime, plasma glucose monitoring and medical nutritional therapy are important aspects of discharge planning.
- On discharge:
  - Rapid reduction in HbA_{1c} especially among those with long standing uncontrolled disease and background retinopathy should be avoided to prevent transient worsening of diabetes retinopathy.[259,260,543 (Level I) 544-546 (Level II-3)]

For further details, refer to the Ministry of Health, Practical Guide to Inpatient Glycaemic Care, 2nd edition, 2020.

Recommendations: Management of T2DM in acute illnesses, stress and surgery

1. In hospitalised patients without known diabetes, plasma glucose >7.8, signifies hyperglycaemia and warrants further monitoring.	*Grade B*
2. Inpatient target plasma glucose levels should be between 7.8 mmol/L-10.0 mmol/L for majority of critically ill and non-critically ill patients.	*Grade B*

6.2 T2DM in adolescents

- T2DM is rapidly increasing among the adolescents (ages 12-18 years) in tandem with rising sedentary lifestyles, prevalence of obesity and increase in-utero glycaemic exposure.[837,838 (Level II-2)]
- T2DM usually occurs in the 2nd decade coinciding with physiologic pubertal insulin resistance, more common in female gender, increased adiposity, family history of diabetes and low socioeconomic status.[839]

- Cross-sectional, observational and therapeutic trials suggest that T2DM in the young might represent a more severe and rapidly progressive disorder than in adults.[840,841 (Level III)]
  - › Obese adolescent T2DM has severe peripheral and hepatic insulin resistance, with approximately 50% lower peripheral insulin sensitivity than age-matched obese peers without diabetes.
  - › β-cells appear to fail at a faster rate (20-35% yearly deterioration)[842,843 (Level II-2)] vs. T2DM in adults (7-11% yearly loss).[844,845 (Level II-2)]
  - › The decline in insulin secretion relative to insulin sensitivity, eventually result in progression to prediabetes and T2DM.[846-849 (Level II-2)]
- Youths with T2DM are expected to have long disease duration and accumulation of glycemia-related complications.
  - › In addition, there is prolonged lifetime exposure to the other atherogenic risk factors, e.g. dyslipidaemia and hypertension.
  - › Current evidence indicates that onset of DKD, neuropathy and retinopathy occur earlier and progressed faster in youth onset T2DM compared with youth-onset T1DM.[850-853 (Level II-2)]
  - › Retinopathy[853 (Level II-2)] and DKD progression[854 (Level II-2)] are likely dependent on the duration of disease and glycaemic control.
- T2DM may be misdiagnosed as T1DM
  - › in non-obese adolescents with diabetes,
  - › when ketosis/ketoacidosis is present at onset;[855,856 (Level III)] or
  - › when pancreatic autoantibodies are positive.[857,858 (Level II-2)]
- Other types of diabetes mellitus may be misdiagnosed as T2DM. These include:
  - › obese T1DM,
  - › T1DM with low autoimmunity; or
  - › monogenic diabetes.

Screening and diagnosis

- Risk-based screening for prediabetes and/or T2DM should be considered in adolescents or during onset of puberty who are overweight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes.[859 (Level III)]
- Screen every 2 years starting at the age of 10 or at onset of puberty, if puberty occurs at a younger age.[860 (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 should be interpreted with caution due to considerable overlap between T1DM, T2DM and monogenic diabetes at onset and within 2 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.

Management

A. Approach to management (Refer Figure 6-1).

- Goal of treatment is to achieve HbA_{1c} <7.0% (<53 mmol/mol; i.e. 8.6 mmol/L).[861] (Level III)
- Home SMBG targets as follows:[861] (Level III)
  - Premeal: 4.0 mmol/L-7.0 mmol/L
  - Post meal: 5.0 mmol/L-10.0 mmol/L
  - Prebed: 4.4 mmol/L-7.8 mmol/L
- HbA_{1c} should be measured every 3 months
- To avoid long-term complications, monitoring as described in Table 6-1 is essential.[862-864] (Level III)

Table 6-1: Essential monitoring in adolescents with T2DM.

Time points	Essential monitoring
At diagnosis and annually	Test for microalbuminuria or macroalbuminuria Examination for retinopathy Test for dyslipidaemia Evaluation for NAFLD Foot examination for neuropathy – foot pulses, pinprick and vibration sensation, ankle reflex.
At every clinic visit	Weight and height BP (hypertensive if BP ≥95th percentile for age, sex and height percentile) at every visit. Inquiry about puberty, menstrual irregularities (PCOS for female adolescence) and obstructive sleep apnoea Psychosocial wellbeing (depression, eating disorder, social adjustment, peer relationships and school performance to determine referral for counselling)[863,864]

NAFLD: non-alcoholic fatty liver disease; BP: blood pressure; PCOS: polycystic ovarian syndrome.

Adapted from Acerini C et al. Pediatr Diabetes 2014.[862] (Level III)

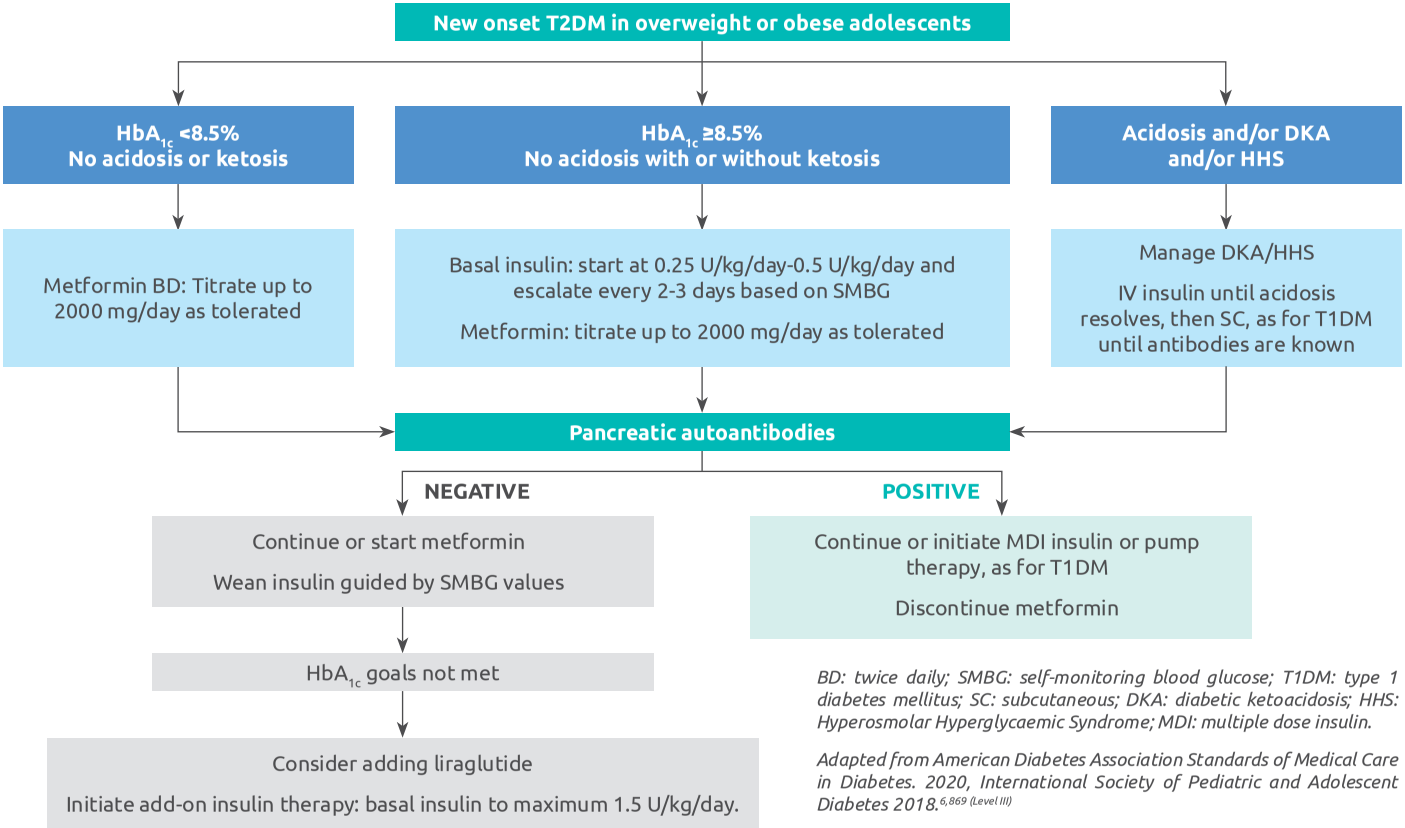
B. General management

- Management of T2DM in adolescents should involve the patient, his/her family and cooperation from school personnel, emphasising healthy parental modelling and conducive surroundings.
- Comprehensive education on self-management and recommendations must be age-appropriate due to complex psychosocial elements and, sensitive to the family's cultural practices and financial resources.
- Comprehensive lifestyle programs that are integrated with diabetes management to achieve 7%-10% decrease in weight in the overweight/obese adolescent.
  - Encourage least 30 min-60 min of moderate-to-vigorous physical activity at least 5 days/week (and strength training at least 3 days/week).
  - Focus on healthy eating patterns i.e. decrease calorie-dense food consumption.
- A multidisciplinary diabetes team, including a physician, diabetes nurse educator, registered dietitian, and psychologist or social worker is important.

C. Pharmacotherapy

- The safety and efficacy of OGLDs in adolescents have not been established.
- Among all the GLDs currently used to treat T2DM in adults, only metformin and insulin are FDA approved for use in adolescents <18 years of age.
- Metformin should be started at 500 mg OD. Gradual dose increment over 3-4 weeks, as tolerated until the maximal dose of 1000 mg BD is achieved.[865]
- 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.[(Level III)]
- If glycaemic targets are not achieved with metformin (with or without basal insulin), liraglutide can be considered[866-868 (Level I)] (avoid in patients with family history of medullary thyroid carcinoma/MEN 2).

Figure 6-1: Approach to initial and subsequent treatment of adolescents with T2DM.



BD: twice daily; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes mellitus; SC: subcutaneous; DKA: diabetic ketoacidosis; HHS: Hyperosmolar Hyperglycaemic Syndrome; MDI: multiple dose insulin.

Adapted from American Diabetes Association Standards of Medical Care in Diabetes. 2020, International Society of Pediatric and Adolescent Diabetes 2018.[6,869 (Level III)]

Recommendations: T2DM 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 recommended.	*Grade C*
3. Metformin and insulin remain the mainstay of T2DM treatment in adolescents.	*Grade A*
4. Incorporation of a multidisciplinary team in managing diabetes in adolescence.	*Grade C*

6.3 T2DM in elderly

- In 2019, it was estimated that the proportion of Malaysian population aged over 65 years was 6.7%.[870]
- Diabetes is more common in the elderly (>60 years old). The prevalence of T2DM in individuals between the ages of 60-64, 65-69 and 70-74 are 42.4%, 43.4% and 40.6%, respectively.[1]
- The elderly with T2DM is a very heterogeneous group ranging from active individuals with little comorbidity and complications to frail individuals with multiple serious co-morbidities and disabling complications.
- There is also an increased rate of age-related concomitant illnesses e.g. hypertension, renal impairment, ischaemic heart disease, cognitive impairment and functional disabilities with increased risk of falls.
- 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.[71,376,871 (Level I)]

- PPG values have been shown to be a better predictor of outcome in elderly patients compared to HbA_{1c} or pre-prandial glucose values.[872 (Level I)]
  - Plasma glucose and capillary plasma glucose should be used instead.
- Greater variability of glucose values is associated with poorer cognition[873 (Level III)] despite equivalent glycaemic control.[334,874 (Level II-3)]
  - Cognitive dysfunction and frailty increase the risk of hypoglycaemia and vice versa.[487,574,875 (Level III)]
- Thus, glycaemic targets will depend on the severity of frailty and overall life expectancy.
- The principle for choice of various OGLDs is similar in the elderly as in younger patients.[876 (Level III)]
  - SUs should be used with caution because of the risk of severe or fatal hypoglycaemia.
  - Risk of hypoglycaemia increases exponentially with age and is higher with glibenclamide than gliclazide and glimepiride.[877 (Level III)]
  - Glibenclamide is not recommended for use in patients with T2DM >60 years of age.[878 (Level III)]
- Similar to OGLDs, the use of insulin in the elderly is associated with increased risk of hypoglycaemia and therefore every effort should be made to minimise the risk.
- Treatment de-escalation or discontinuation should be considered once organ failure develops or end of life care is initiated.[879 (Level III)]
- Institutionalised elderly patients have impaired hormonal regulation and counter-regulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy and slowed intestinal absorption.[880 (Level III)]
- Optimal nutrition and protein intake (at least 1.5 g/kg/d - 15%-20% of the total caloric intake), regular exercise with resistance training may be instituted to increase muscle strength and quality to prevent sarcopenia.[881-883 (Level III)]
  - This reduces the risk of fall secondary to frailty.
- Regular assessment of medical, psychosocial, functional and social domains is necessary.
  - Annual screening with tools such as the Mini-Mental State Examination,[884] Mini-Cognitive,[885] the Montreal Cognitive Assessment[886] and the Clinical Frailty Score[887 (Level II)] may help identify patients requiring neuropsychological evaluation and referral to geriatrician, especially for those in whom dementia is suspected.

- Other co-morbidities should also be treated to goal.
  - Lipid-lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary or secondary prevention trials.

Table 6-2: Treatment goals for glycaemia, BP and dyslipidaemia in elderly with T2DM.

Patient characteristics / health status	Rationale	Reasonable HbA_{1c} goal[‡]	Plasma glucose targets (mmol/L)	BP (mm Hg)	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer life expectancy	≤7.5	Fasting: 5-7.2 Pre-bed: 5.0-8.3	<140/90	Statins treatment as long as tolerated.
Complex/ intermediate (multiple coexisting chronic illnesses* or mild-to moderate cognitive and functional impairment)	Intermediate life expectancy, high treatment burden, hypoglycaemia vulnerability, fall risk	<8.0	Fasting: 5-8.3 Pre-bed: 5.6-10	<140/90	
Very complex/ poor health (long-term care or end stage chronic illnesses** or moderate-to-severe cognitive and functional impairment)	Limited life expectancy makes benefit uncertain	<8.5	Fasting: 5.6-10 Pre-bed: 6.1-11.1	<150/90	Individualised. Consider likelihood of benefits of statins especially for 2° prevention

*[‡] A lower HbA_{1c} 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 DKD, MI and stroke. "Multiple" means ≥3, but many patients may have ≥5. ** The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, DKD requiring dialysis, or uncontrolled metastatic cancer, which significantly reduce life expectancy.*

Adapted from American Diabetes Association Standards of Medical Care Diabetes 2020.[6 (Level III)]

Recommendations: T2DM in elderly

1. PPG values are a better outcome predictor compared to HbA_{1c} or pre-prandial glucose values.	*Grade C*
2. Glycaemic targets depend on the degree of frailty and overall life expectancy of each individual, rather than chronological age.	*Grade C*
3. Adequate nourishment and physical training to be established.	*Grade C*
4. Periodic cognitive assessment to determine adherence to prescribed management.	*Grade B*

6.4 Diabetes in Ramadan

- Fasting during Ramadan is obligatory for all healthy adult Muslims.
- Ramadan fasting may have favourable physiological changes among healthy individuals, such as decreased body weight and lipid profile.
- Fasting in certain individuals with diabetes may be associated with adverse outcomes; hence they are not obliged to fast.
  - However, many patients with diabetes choose to fast as shown in the Epidemiology of Diabetes and Ramadan (EPIDIAR) study,[888 (Level II-2)] despite a clear instruction from the Quran on individuals who are exempted from fasting (Surah Al Baqarah Verse 184-185).
- Management of Muslim patients with T2DM during Ramadan continues to be a challenge for healthcare professionals.[889 (Level II-2)]
- There are several potential risks associated with fasting in Ramadan namely hypoglycaemia, hyperglycaemia/DKA, dehydration and thrombosis.
- It is important to categorise patients who intend to fast based on risk stratification as listed in Appendix 11. Those in high- and very high-risk categories should abstain from fasting.[890,891(Level III)]

Preparation prior Ramadan

- A pre-Ramadan medical assessment should be performed to categorise patients in terms of risks of fasting as well as to optimise their management. These include:
  - general well-being,
  - diabetes medications,
  - glycaemic control,
  - comorbidities; and
  - complications.
- Patients and caregivers should receive education concerning self-care regarding the following:[892-894 (Level III)]
  - risks of adverse effect of fasting,
  - SMBG,
  - indications for termination of fasting,
  - meal planning, food choices and fluid intake,
  - exercise and physical activity; and
  - modifications of glucose lowering medication (oral and in particular insulin).
- Risks of adverse effect of fasting
  - There are several potential risks associated with prolonged fasting. It is therefore important to increase patient awareness and to reduce risks while, if possible, enabling patients to participate in their spiritual experience of fasting during Ramadan.
  - Adverse effects and risks associated with fasting include:
    - hypoglycaemia, especially during the late period of fasting before iftar,
    - severe hyperglycaemia after each of the main meals,
    - dehydration,
    - acute kidney injury in patients prone to dehydration, particularly elderly patients and those with impaired kidney function.
- These diabetes-related risks can be minimised through education, appropriate food choices and SMBG.

During Ramadan

A. Plasma glucose monitoring

- Patients are advised to monitor their plasma glucose and most importantly when symptomatic of hypoglycaemia.
- The frequency of SMBG depends on risk factors and current medications.
  - For those at moderate or low risk, this may be once or twice a day.
  - Those at high or very high risk should check their plasma glucose levels several times a day.

- › Patients on insulin and/or SUs may need to monitor their plasma glucose levels more frequently.

- The frequency of plasma glucose testing is dependent on the insulin regimen and/or the risk of hypo- or hyperglycaemia.

B. Indications for termination of fasting (Refer to Table 6-3)

Table 6-3: Criteria to terminate fasting.

Plasma glucose (mmol/L)	Time of day
<3.3[895] (Level II-2)	Anytime during fast
<3.9[894,896] (Level II-2)	Within 1st few hours of fasting; in particular, if on SUs, meglitinides or insulin
>16.7[895] (Level II-2) **or symptomatic of dehydration**	Anytime during fast
Without SMBG (Level III)	When experiencing symptoms of hypoglycaemia, or severe dehydration, e.g. giddiness, syncope or confusion

C. Meal planning, food choices and fluid intake

- Recommendations for ***Sahur*** (pre-dawn meal)[897] (Level III)
  - › Should never be omitted.
  - › Should consist of a balanced meal with adequate CHO.
  - › To be taken as late as possible, just before Imsak (dawn).
  - › Intake of salty foods should be avoided to reduce risk of dehydration.

- Recommendations for ***Iftar*** (breaking of fast at sunset)[897] (Level III)
  - › It should not be delayed.
  - › Intake of high-sugar foods should be avoided. However, 1-2 kurma (dates) at the start of *Iftar* following the practice of the Prophet (Sunnah) may be taken as part of CHO exchange.
  - › Sufficient fluid should be taken to replenish fluid loss during the day. Aim for 8 glasses of fluid a day.
  - › The main meal is encouraged after the performance of Maghrib prayers.

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

D. Exercise and physical activity

- Physical activity and exercise need to be adjusted during Ramadan.

- The following are recommended:[894,898] (Level III)
  - › light and moderate intensity exercise on a regular basis,
  - › avoid rigorous exercise during the day because of the risk of hypoglycaemia,

› the timing of exercise is preferably performed 1-2 hours after *Iftar*,
› performance of *Tarawih* prayers is a form of physical activity.

E. Modification of GLDs

- Glucose-lowering therapies should be individualised during fasting.[889 (Level II-2)]
- Glucose-lowering therapies of choice are those with low risk of hypoglycaemia and do not require modification with regards to dose and timing of administration.
- OGLDs:
  › The preferred OGLDs are those which have low risk of hypoglycaemia.
  › OGLDs which have been proven to be safe in Ramadan include:[891,899 (Level III) 900 (Level II-2)]
    - Metformin
    - Glimepiride
    - Gliclazide
    - Sitagliptin
    - Vildagliptin[901 (Level II-1)]
  › SGLT2-i[902-905] has lower risk of hypoglycaemia, but are associated with some safety concerns in particular, dehydration and should be used with caution in patients with DKD ≥Stage 3.[891 (Level III) 905 (Level II-3)]
  › The principles of OGLD modifications are:
    - the non-fasting morning dose should be taken during *Iftar*, and the non-fasting evening dose should be taken during *Sahur*, and
    - the dose of glucose-lowering agents may be maintained or reduced depending on risk of hypoglycaemia.

Table 6-4: Recommendations for SMBG during Ramadan.

Mode of treatment	*Sahur*		Mid-day	*Iftar*	
	Pre	Post		Pre	Post / Pre-bed
OGLDs (especially SU)			√	√	√
Insulin					
Basal	√		√	√	
Premixed BD	√	√	√	√	√
Prandial/bolus	√	√	√	√	√

Table 6-5: Adjustment of OGLDs during fasting in Ramadan

Regimen	*Iftar*	*Sahur*
AGIs	No change	No change
Biguanides (metformin)	No change	No change
DPP-4i	Switch timing to *Iftar*	
Meglitinides	No change	No change
SUs	No change	*Glibenclamide:* reduce/omit *Gliclazide:* reduce/omit/switch timing to *Iftar* *Gliclazide MR:* switch timing to *Iftar*/may need to reduce dose *Glimepiride:* switch timing to *Iftar*/may need to reduce dose
SGLT2-i*	Switch timing to *Iftar*	
TZDs	No change	

AGIs: Alpha-glucosidase inhibitors; DPP4-i: Dipeptidyl peptidase-4 inhibitors; SU: sulphonylurea; SGLT2-i: sodium-glucose transport protein 2 inhibitor; TZDs: thiazolidinediones. Based on the expert opinion of this CPG's committee.[(Level III)]

- Injectable glucose lowering therapies
  - Liraglutide[906] (Level II-1) and exenatide are safe as an add-on treatment to metformin and can be effective in reducing weight and HbA_{1c} levels during Ramadan.
  - Data relating to the use of newer GLP1-RAs (lixisenatide and dulaglutide) during Ramadan are lacking.
  - No dose modification is required, and injection should be given at *Iftar*.
- Insulin therapy
  - Insulin use during prolonged fasting carries an increased risk of hypoglycaemia.
  - Use of insulin analogues is preferred over regular human insulin due to a number of advantages that include less hypoglycaemia.
  - Individualised adjustments of insulin dose and timing will need to be implemented when fasting during Ramadan. In those who are prone to developing hypoglycaemia, insulin analogues may be a better alternative.[889] (Level II-2)

Table 6-6: Insulin adjustments during Ramadan.

Insulin Regimen	Adjustment
Basal insulin only	Basal insulin to be taken at bedtime or after *Iftar*. May need dose reduction if there is a risk of daytime hypoglycaemia. Patients who are well/tightly controlled suggest dose reduction of 15-30%[890 (Level III)]
Premixed insulin once daily	Inject usual dose at *Iftar*.
Premixed insulin twice daily	Reverse doses – Morning dose given at Iftar and evening dose at Sahur. *Iftar:* Give morning dose – dose may need to be adjusted *Sahur:* Insulin dose reduced by 20-50% to prevent daytime hypoglycaemia. **OR** change to short/rapid acting.
Basal bolus insulin **Basal Insulin**	Taken at bedtime or any time after *Iftar*. May require a dose reduction if there is daytime hypoglycaemia.
Prandial/bolus insulin	*Sahur:* Adjust according to CHO intake. May require dose reduction to avoid post meal hypoglycaemia Lunch: Omit. *Iftar:* Dose adjustment according to CHO intake. Insulin should be taken before the main meal.
Insulin pump	Basal insulin rate: May require reduction of up to 25%. Prandial bolus: According to individualised insulin-to-carbohydrate ratio (ICR).

Adapted from Al-Arouj M, et al. Diabetes Care 2010; Pathan MF et al. Indian J Endocrinol Metab 2012; Hui E, et al Diabetes Metab Res Rev 2010; Bin-Abbas BS Ann Saudi Med 2008; Hawli YM, et al Curr Ther Res Clin Exp 2009; Benbarka MM et al Diabetes Technol Ther 2010; Ministry of Health Malaysia Practical Guide to Insulin Therapy in Type 2 diabetes mellitus 2010.[282,889,895,907-910]

Post Ramadan visit

- A post-Ramadan follow-up meeting with HCPs is advisable in order to discuss medication and regimen readjustments and assess how the patient handled the fasting.
- It should be stressed to the patient that a safe fast one year does not automatically make them a low risk for the next year due to the progressive nature of the disease.

Recommendations: Management during Ramadan

1. A pre-Ramadan medical assessment of general well-being, glycaemic control, comorbidities and complications should be performed to categorise the patient's risk from fasting as well as to optimise their managements.	*Grade C*
2. Patients and caregivers should receive education concerning self-care on risks of hypoglycaemia, hyperglycaemia and dehydration.	*Grade C*
3. Glucose lowering therapies should be individualised during fasting – modification of medication may be needed.	*Grade C*
4. SMBG recommended especially in patients on insulin or SUs/meglitinides.	*Grade C*
5. Clear advice on when to terminate fasting should be given e.g.in the event of severe hypoglycaemia or during "sick day".	*Grade C*

SECTION 7

PREVENTION OF T2DM

SUMMARY OF UPDATES

- Individuals with pre-diabetes are at risk of progression to frank diabetes and are also at higher CV risk.
- The mainstay of T2DM prevention is intensive behavioural lifestyle intervention program to achieve target weight loss of at least 7% (and improving insulin resistance).
- Metformin should be considered in those at very high risk, prediabetes, previous history of GDM or for those who failed lifestyle therapy after 6 months.
- Newer therapeutic agents, e.g. high dose liraglutide, in obese prediabetic individuals have been shown to result in weight reduction and delay progression to T2DM.

7.1 For people at risk

- There are many risk factors that predispose an individual or population to developing glucose intolerance and eventually diabetes (Refer to Tables 2-1 & 2-2).
- There is ample evidence that lifestyle related changes as a result of rapid urbanisation are influencing the explosion of T2DM. In particular weight gain and a sedentary lifestyle.
- As T2DM is an endpoint in the glucose tolerance continuum, it is possible to halt this slide from normal to IGT and subsequently T2DM.

7.2 For people with prediabetes

- Patients with IFG and/or IGT and/or HbA_{1c} 5.7%-6.2% are considered as having prediabetes.
- Prediabetes increases the risk of progression to T2DM. In addition, patients with prediabetes have a higher risk of CVD.

- Progression to diabetes in patients with prediabetes can be delayed.
- Patients with prediabetes often have other CV risk factors, e.g. hypertension and dyslipidaemia,[911] and, are associated with increased CV risk.[912] They should be screened for presence of these modifiable CV risk factors, and appropriate management instituted.

Interventions proven to reduce the conversion of IFG/IGT to T2DM

A. Lifestyle modifications

- Diet and moderate intensity physical activity remain the mainstay of therapy.[53,913-916 (Level I)]
- There is strong evidence that combination of diet plus physical activity reduces or delays the incidence of T2DM in prediabetes, particularly in IGT patients.[917 (Level I)]
- Intensive behavioural lifestyle intervention program modelled on the Diabetes Prevention Program (DPP) should be advocated for all prediabetic patients to achieve moderate-intensity physical activity (such as brisk walking) for at least 150 min/week and a target weight loss of at least 7%.[6 (Level III)]
- Based on intervention trials, Mediterranean, low-calorie, low-fat eating plans may be beneficial for prediabetes with an emphasis on high dietary fibre, whole grains, legumes, nuts, fruits and vegetables, and minimal refined and processed foods.[6,918 (Level III)]
- Interventions that use technology to disseminate diet and exercise lifestyle programs have been shown to be effective in weight reduction and improvements in glycaemic levels in patients with prediabetes and should be considered as part of T2DM prevention strategy.[6 (Level III) 919 (Level I)]
- There is limited evidence on benefit of bariatric surgery on reduction of progression to T2DM.[920 (Level I) 921 (Level II-2)]

B. Pharmacotherapy

- In addition to lifestyle intervention, metformin should be considered for those at very high risk. These include those with:[6,914,922 (Level I)]
  - › combined IFG and IGT,
  - › IGT + obesity (BMI >35 kg/m^2),
  - › IGT + <60 years old,
  - › FPG >6.1 mmol/L,
  - › HbA_{1c} >6%,
  - › previous history of GDM; or
  - › for those who failed lifestyle therapy after 6 months (refer to Figures 3-3 and 3-4).

- Metformin reduces progression from prediabetes to T2DM by ~30%[914,922 (Level I)] with persistent benefit, especially in women with previous GDM (overall risk reduction 18%) over the 10 years of the DPP/DPPOS program.[923 (Level II-2)]
- Metformin is the only drug that has received endorsement by our Malaysian Regulatory authority as well as by other national guidelines for the prevention of T2DM.[6,924]
- Refer Table 7-1 for other pharmacological interventions that have been shown to delay the onset of T2DM.
- There is no firm evidence that DPP-4i and SGLT-2i compared with placebo, substantially influence the rate of progression to T2DM.[925,926 (Level I)]

Table 7-1: Pharmacological interventions proven to delay progression to T2DM

Pharmacological agents	May prevent/delay development of T2DM in:
Liraglutide[925 (Level I)]	Liraglutide 3mg/day delays progression to T2DM in prediabetic patients with obesity (BMI >27 kg/m^2 + IGT, IFG, or HbA_{1c} >5.7%)
AGIs[927 (Level I)]	May prevent or delay the development of T2DM in people with IGT.
Pioglitazone[928 (Level I)]	Reduces the development of T2DM predominantly in those with initial IFG and HbA_{1c} of >5.7%.
Orlistat[929 (Level I)]	Beneficial in patients with IGT and BMI >28kg/m^2 as management of obesity for a minimum duration of 12 weeks.

T2DM: type 2 diabetes mellitus; BMI: body mass index; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; AGIs: alpha glucosidase inhibitors.

Recommendations: Prevention of T2DM

1. The mainstay of diabetes prevention is intensive behavioural lifestyle intervention program to achieve target weight loss of at least 7%.	*Grade A*
2. Metformin should be considered in those at very high risk, prediabetes, previous history of GDM or for those who failed lifestyle therapy after 6 months.	*Grade A*

SECTION 8

COMPLEMENTARY AND ALTERNATIVE THERAPY IN T2DM

SUMMARY OF UPDATES

- There is insufficient evidence to recommend the use of supplements such as chromium, vitamin D, cinnamon or herbs/supplement.
- Alternative therapies may contain harmful ingredients, may be unsafe or may be improperly marketed as over-the-counter (OTC) products.
- A recent prospective RCT assessing vitamin D supplementation failed to slow progression of prediabetes to overt diabetes.

8.1 Complementary and alternative medicine (CAM)

- Complementary and alternative medicine (CAM) is defined as healthcare management outside of conventional medicine, with "complementary" meaning used together with, and "alternative" meaning used in place of conventional medicine.[930]
- The 2020 American Diabetes Association guidelines state that there is insufficient evidence to recommend the daily use of supplements such as chromium, vitamin D, cinnamon or herbs/supplement.[6] (Level III)
- Many individuals with diabetes are hesitant to inform their healthcare providers of their complementary therapy use.[931] (Level III)
  - › Unfortunately, alternative therapies may contain harmful ingredients, may be unsafe or may be improperly marketed as OTC products when they should be marketed as prescription products.
- Healthcare providers are encouraged to enquire about the use of CAM in people with diabetes.[40] (Level III)
- It is very important to advise patients not to replace conventional medical therapy for T2DM with an unproven alternative therapy.
  - › Patients need to be cautioned on the potential side effects, drug interactions and lack of product standardisation.

  - In addition, the increased costs that patients may incur when they use ineffective therapies or delay treatment with proven therapeutic agents.

- Natural health products which are unlabelled should not be used to avoid intake of products that may be adulterated with pharmaceuticals or other contaminants.[40 (Level III)]

- Medicines for T2DM and other health conditions may need to be adjusted if a person is taking an alternative treatment as drug-herb interactions may occur.

Popular supplements and evidence of benefits

- Clear scientific evidence supporting the benefit from all herbal, vitamin and other supplementations for treatment and prevention of T2DM remain scarce.
  - Olive oil: When taken as supplementation or part of a Mediterranean diet, has demonstrated favourable effects in reducing the risk of development of T2DM in prediabetes and improvement in glycaemic control in T2DM by 0.27%.[932 (Level I)]
  - Vitamin D: Although earlier observational studies have shown an association between low level of vitamin D and increased risk for T2DM, however, a recent RCT study on vitamin D supplementation **failed** to delay progression to T2DM.[933 (Level I)]
  - Vitamin E,[934 (Level I)] cinnamon,[935 (Level I)] curcumin:[936 (Level I)] These have no significant benefit on glycaemic control in patients with T2DM.

Note on acupuncture: Acupuncture has not been shown to improve glycaemic control in patients with T2DM.

8.2 Reporting adverse events

- 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 *www.npra.gov.my/index.php/en/health-professionals/reporting-adr*[937]

Recommendations: Complementary and alternative therapy

1. Healthcare providers should enquire about the use of CAM therapies in patients with prediabetes and T2DM.	*Grade C*
2. Benefits from all herbal, vitamin and other supplementations for treatment and prevention of T2DM remain unclear.	*Grade C*

SECTION 9

KEY PERFORMANCE INDICATORS

SUMMARY OF UPDATES

- This section has been revamped and focuses on key performance indicators for management of T2DM.
- Two measures specific for KPIs and 3 measures for baseline data collection have been introduced.
- The results will allow for future re-strategizing where discrepancies and imbalances exist. It will also allow for sharing of best practices contributing to achieving higher standards of care.

9.1 Guide to Key Performance Indicators (KPI)

- Over the years, the MOH has been monitoring processes and key indicators (clinical and biochemical) – particularly in the public sector.
- The priority should be on coordinated care to maximise use of limited resources.
- To analyse clinical outcomes that matter:
  - the data should be collected and expressed as "outcomes per population" by region (district, state, specified geographical region, national),
  - results will allow for future re-strategizing where discrepancies and imbalances exist. This is important for sharing of best practices that contribute to achieving higher standards of care particularly in regions performing below average.
  - interventions to promote patient centred multi-level care (between primary and secondary care; between different disciplines; between private and public).
- The data collected should include parameters that fulfil the following:
  - key clinical outcomes,
  - easy to collect; and
  - collected without the intervention of the direct stakeholders.

Figure 9-1: Key performance indicators for management of T2DM

$$\text{Percentage of T2DM patients (at >12- month follow-up) with } HbA_{1c} > 8.5\% = \frac{\text{Number of T2DM patients with } HbA_{1c} > 8.5\%}{\text{Total number of T2DM (at >12-month follow up) patients attending the facility}} \times 100\%$$

**(Proposed Target: <20% for primary care & 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)*

**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.*

9.2 Baseline data collection

The following are for data collection to enable future planning of T2DM care.

Figure 9-2: Baseline data collection

A. Number of new cases of patients with T2DM needing renal replacement therapy (RRT) per year per 100000 total population.

$$\text{No. of new cases of T2DM needed RRT/year/100,000 total population} = \frac{\text{No. of new T2DM cases needing RRT*}}{\text{Total population}}$$

**Collected from public and private hospitals, and renal dialysis centres in that region for one year*

B. Number of below knee amputations (BKA) in patients with T2DM per year per 100000 total population.

$$\text{No. of BKA in patients with T2DM/year/100,000 total population} = \frac{\text{No. of BKA in patients with T2DM*}}{\text{Total population}}$$

**Collected from the operating theatre of all private and public hospitals in that region for one year.*

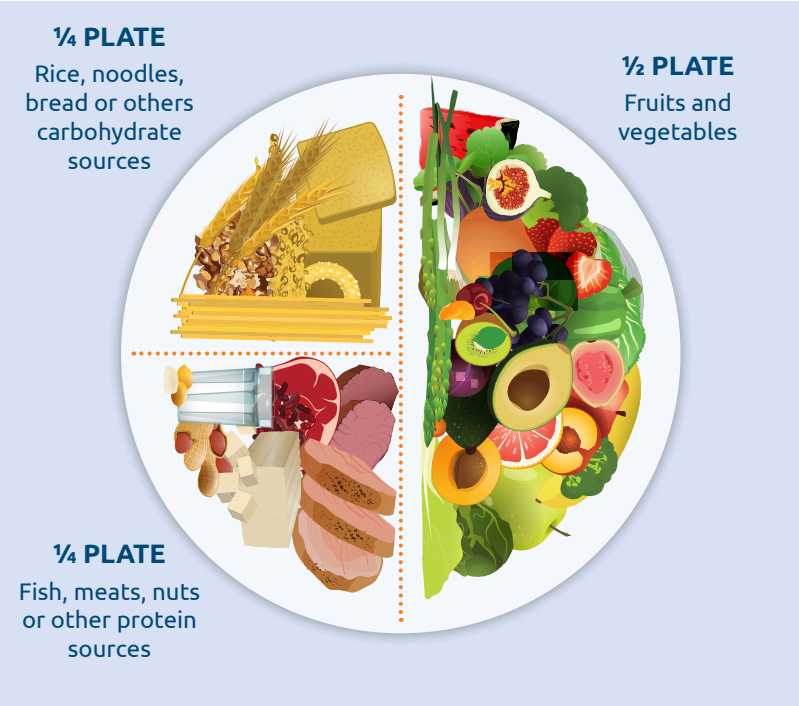
C. Number of severe hypoglycaemic admissions in patients with T2DM per year per 100000 total estimated population with T2DM (based on latest National Health and Morbidity Survey data).

$$\text{No. of severe hypolycaemic admissions in patients with T2DM/year/100,000 total population} = \frac{\text{No. of severe hypolycaemic admissions in patients with T2DM*}}{\text{Total estimated population with T2DM}}$$

**Collected from all private and public hospitals in that region for one year.*

APPENDIX 1

MALAYSIAN HEALTHY PLATE



Adapted from Ministry of Health Malaysia, Nutrition Department.[938 (Level III)]

APPENDIX 2

CARBOHYDRATE CONTENT OF COMMON MALAYSIAN FOODS

Foods	Serving	Calories (kcal)	CHO content (g)	Approx. CHO exchanges*
Cooked rice	1 bowl (159 g)	207	48	3
Nasi lemak	1 small packet (200 g)	338	51	3.5
Fried rice	1 plate (200 g)	386	53	3.5
Roti canai	1 piece (95 g)	301	46	3
Chappati	1 piece (100 g)	300	47	3
Curry mee	1 bowl (450 g)	549	55	4
Fried noodles (mee/meehoon)	1 plate (200 g)	346	48	3
Bread (white/ wholemeal)	1 slice (30 g)	70	15	1
Biscuits, unsweetened	2 pieces (18 g)	80	14	1
Kuih lapis	1 piece (100 g)	152	33	2
Curry puff	1 piece (40 g)	128	17	>1
Potato	1 medium (90 g)	90	16	1
Dhal (raw)	½ cup (98 g)	98	64	4
Full cream milk	1 cup (250 ml)	187	18	1
Low fat milk	1 cup (250 ml)	131	12	1
Skim milk powder	4 tablespoons (28 g)	100	16	1
Condensed milk, sweetened	2 tablespoons (40 g)	126	21	1.5
Tea with condensed milk (Teh tarik)	1 mug (250 ml)	220	36	>2
Coffee with sugar (Kopi O)	1 mug (250 ml)	198	50	>3
Chocolate flavoured beverage	1 mug (250 ml)	277	46	3

Fruit flavoured drink	1 glass (250 ml)	113	28	2
Tea with milk, sugar and tapioca balls (Bubble tea)	1 small serving (473 ml)	299	80	>5
Apple/orange	1 medium (114 g)	40	9	<1
Banana (pisang mas)	1 small (50 g)	40	9	<1
Star fruit	1 medium (260 g)	56	11	1
Durian local	3 pieces, no seed (189 g)	83	15	1
Langsat/grapes/ longan	8 small (233 g)	52	12	1
Guava	½ fruit (100 g)	50	11	1
Watermelon/ papaya/ pineapple	1 slice (160 g)	56	11	1
Mango	1 small (100g)	50	11	1

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

Sourced from Tee ES, et al. 1997, Suzana S et al. 2015, Min JE et al. 2017.[939-941 (Level III)]

APPENDIX 3

FOOD GROUPS AND EXCHANGE LISTS

Cereals, Grain Products and Starchy Vegetables (Each item contains 15 g CHO, 2 g protein, 0.5 g fat and 75 calories)	
Cereals, Grain & Bread	
Rice, white unpolished (cooked)	½ cup or ⅓ Chinese rice bowl
Can be exchanged with	
Rice porridge	1 cup
Kway teow	½ cup or 1/3 Chinese rice bowl
Mee hoon	
Tang hoon	
Spaghetti	
Macaroni	
Mee, wet	⅓ cup
Idli	1 piece (60 g)
Putu mayam	1 piece (40 g)
Thosai, diameter 20 cm	½ piece
Chappati, diameter 20 cm	⅓ piece
Bread (wholemeal, high fibre, white/brown)	1 slice (30 g)
Plain roll	1 small (30 g)
Burger bun	½ piece
Pita bread, diameter 6 inches	½ piece
Oatmeal, cooked	¼ cup
Oats, uncooked	3 rounded tablespoons
Muesli	¼ cup
Flour (wheat, rice, atta)	3 rounded tablespoons
Biscuits (plain, unsweetened) e.g. cream crackers, Ryvita	3 pieces
Small thin, salted biscuits (4.5 x 4.5 cm)	6 pieces

Starchy Vegetables	
*Baked beans, canned	⅓ cup
*Lentils	⅓ cup
Can be exchanged with	
Corn kernel (fresh/canned)	½ cup
Peas (fresh/canned)	½ cup
Sweet potato	½ cup (45 g)
Tapioca	
Yam	
Breadfruit (sukun)	1 slice (75 g)
Pumpkin	1 cup (100 g)
Corn on the cob, 6 cm length	1 small
Potato	1 small (75 g)
Potato, mashed	½ cup
Water chestnut	4 pieces

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

Fruits (Each item contains 15 g carbohydrate and 60 calories)	
Fruits	
Orange	1 medium
Can be exchanged with	
Banana	1 small (60 g)
Apple	1 medium
Custard apple (buah nona)	
Star fruit	
Pear	
Peach	
Persimmon	
Sapodilla (ciku)	
Kiwi	
Hog plum (kedondong)	6 whole
Mangosteen	2 small
Plum	2 small

Duku langsat	8 pieces
Grapes	
Langsat	
Longan	
Water apple (jambu air), small	
Lychee	5 whole
Rambutan	5 whole
Pomelo	5 slices
Papaya	1 slice
Pineapple	
Watermelon	
Soursop (durian belanda)	
Guava	½ fruit
Cempedak	4 pieces
Jack fruit (nangka)	4 pieces
Prunes	3 pieces
Dates (kurma), dried	2 pieces
Raisin	20 g
Durian	2 medium seeds
Mango	½ small

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)				
	CHO (g)	Protein (g)	Fat (g)	Energy (kcal)
Lean meat/Meat substitutes	0	7	4	65
Fish/Shellfish	0	7	1	35
Lean Meat				
Chicken (raw, without skin)	½ drumstick			
Can be exchanged with				
Lean meat (all varieties)	1 small serve (40 g)			
Poultry (young)	40 g raw/30g 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)				
Fresh cow's milk	1 cup (240 ml)			
UHT fresh milk				
Powdered milk (skim, full cream)	4 rounded tablespoons or 1/3 cup			
Yogurt (plain/low fat)	¾ cup			
Evaporated (unsweetened)	½ cup			
Milk nutrient levels- 1 cup/240 ml				
	CHO (g)	Protein (g)	Fat (g)	Energy (kcal)
Skimmed	15	8	Trace	90
Low fat	12	8	5	125
Full cream	10	8	9	150

Fat (Each item contains 5 g of fat and 45 calories. Some of the foods in the list, e.g. nuts and seeds also contain small amounts of carbohydrate and protein)	
Oil (all types)	1 level teaspoon (5 g)
Can be exchanged with	
Butter, margarine	1 level teaspoon
Mayonnaise	
Shortening, lard	
Peanut butter (smooth or crunchy)	2 level teaspoons
Cream, un-whipped (heavy)	1 level teaspoon
Cream cheese	
Salad dressing	
Cream, un-whipped (light)	2 level teaspoons
Coconut, shredded	
Coconut milk (santan)	
Non-dairy creamer, powder	
Plum	2 small
Duku langsat	8 pieces
Almond	6 whole
Cashew nut	6 whole
Walnut	1 whole
Peanut	20 small
Sesame seed	1 level tablespoon
Watermelon seed (kuachi) with shell	¼ cup

Adapted from Malaysian Medical Nutrition Therapy Guidelines for T2DM, 2013.[82 (Level III)]

APPENDIX 4

GLYCAEMIC INDEX OF FOODS

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

GI = glycaemic index.

Adapted from Atkinson FS et al. 2008, Foster-Powell K et al. 2002, Mohd Yusuf BN et al. 2008, Shanita SN, et al. 2011, Robert SD, et al. 2008.[942-946 (Level III)]

APPENDIX 5

ASSESSMENT PRIOR TO INTENSE EXERCISE

General assessment	• Elicit careful history and assess CV risk factors. • Assess for conditions that might contraindicate certain types of exercise or predispose to injury. • Patient's age and previous physical activity level should be considered to customise exercise regimens according to individual needs.
CVD	• CV assessment should include a full history for CV 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. • CV assessment is recommended for patients with autonomic neuropathy and/or albuminuria (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	• Avoid vigorous intensity aerobic or resistance exercise in presence of proliferative (or severe non-proliferative) retinopathy because of the risk of vitreous haemorrhage or retinal detachment. • Consultation with an ophthalmologist prior to engaging in an intensive exercise regimen may be appropriate.
DKD	• There is no evidence for specific restriction of exercise. • Importantly, CVD is increased in individuals with albuminuria/DKD, so CV assessment is recommended prior to exercise.

Plasma glucose	• Check plasma glucose before exercise. • If pre-exercise plasma glucose is low normal (<5.6 mmol/L), advisable to take extra CHO before exercise. This may not be necessary for short duration exercise or for those who are not taking insulin or insulin secretagogues.

CVD: cardiovascular disease; CV: cardiovascular; DKD: diabetic kidney disease; CHO: carbohydrate.

Adapted from the American Diabetes Association Standards for Medical Care in Diabetes 2020.[6 (Level III)]

APPENDIX 6

GRADING OF PHYSICAL ACTIVITIES AND METABOLIC EQUIVALENT TARGETS

Moderate activities	Strenuous activities
Faster walking (3-4.5 mph)	Race-walking, jogging or running (5 mph-7 mph or approximately 8.0 km/hr-11.3 km/hr)
Cycling 5 to 9 mph, level terrain, or with few hills,	Cycling uphill, >10 mph or approximately >16 km/hr
Gardening and yard work: raking the lawn, trimming shrubs and trees, planting trees	Gardening and yard work such as shovelling hay, digging ditches and carrying heavy loads, swinging an axe
Moderate housework: walking downstairs, doing heavy laundry, scrubbing the floor or bathtub while on hands and knees	Climbing stairs while carrying household items weighing 25 lbs (11 kg) or more
Ballroom dancing, line dancing, square dancing, folk dancing, modern dancing, disco Swimming- recreational, snorkelling	Swimming-steady paced laps, water jogging, scuba diving
Badminton (non-competitive)	Playing singles tennis, squash, racquet ball, football, soccer, rugby, basketball
Aerobics (low impact)	Jumping rope
Doing water aerobics	Canoeing or rowing, kayaking.
Playing doubles tennis	

Mph: miles per hour; km/hr: kilometre per hour; lbs: pounds; kg: kilogram.

Metabolic equivalent targets (METS) are defined as:
Moderate Intensity: *50%-70% of a person's maximum heart rate. (3.0-5.9 METs)*
Vigorous / Strenuous Intensity: *>70% of a person's maximum heart rate. (≥6.0 METs)*

The ratio of exercise metabolic rate. One MET is defined as the energy expenditure for sitting quietly, which, for the average adult, approximates 3.5 ml of oxygen uptake per kilogram of body weight per minute (1.2 kcal/min for a 70-kg individual). For example, a 2-MET activity requires two times the metabolic energy expenditure of sitting quietly.

Muscle strengthening exercise or resistance exercise
Activities to increase muscle strength and endurance for minimum of 3 times per week: • Should be progressive • Involving major muscle groups • Repetitive • e.g. Lifting weights – dumbbells or barbells

Adapted from American College of Sports Medicine Position Stand. Progression Models in Resistance Training for Healthy Adults, 2009.[947 (Level III)]

APPENDIX 7

DOSAGE OF GLUCOSE LOWERING DRUGS IN CHRONIC KIDNEY DISEASE (CKD)

Generic Name	Usual dose*	Dose adjustment in renal failure			
		Mild (CKD 2) (GFR 60-89)	Moderate (CKD 3) (GFR 30-59)	Severe (CKD 4 & 5) (GFR <30)	
Biguanide§					
Metformin	500-1000 mg BD	Continue	50% dose reduction	Avoid	
Sulphonylurea^					
Glibenclamide	5 mg OD -10 mg BD	Use with caution	Avoid		
Gliclazide	80 mg OD -160 mg BD	No dose adjustment		Caution	
Gliclazide MR	30-120 mg OD	No dose adjustment		Caution	
Glimepiride	1-6 mg OD	Initiate with 1 mg OD		≥15: Caution	<15: Avoid
Glipizide	2.5 mg OD -10 mg BD	No dose adjustment		Caution	
Meglitinides					
Repaglinide	0.5-4 mg TDS	No dose adjustment		Initiate at 0.5 mg with meals	
Alpha-glucosidase Inhibitor					
Acarbose	25-100 mg TDS	50-100%		≥25: 50-100%	<25: Avoid
Thiazolidinediones					
Pioglitazone	15-45 mg OD	No dose adjustment **(caution with fluid retention risk)**			
DPP4-i					
Sitagliptin	100 mg OD	No dose adjustment	> 50: No dose adjustment 30-<50: 50 mg OD	25 mg OD	
Vildagliptin	50 mg OD-BD	No dose adjustment	≥50: No dose adjustment <50: 50 mg OD (limited data)		
Saxagliptin	2.5-5 mg OD	No dose adjustment	>50: No dose adjustment ≤50: 2.5 mg OD		
Linagliptin	2.5-5 mg OD	No dose adjustment			

Generic Name	Usual dose*	Dose adjustment in renal failure			
		Mild (CKD 2) (GFR 60-89)	Moderate (CKD 3) (GFR 30-59)	Severe (CKD 4 & 5) (GFR <30)	
GLP-1RA					
Exenatide IR	5 µg/20 µL; 10 µg/40 µL	No dose adjustment	>50: No dose adjustment 30-50: Caution in initiating or escalating dose from 5 to 10 mcg	Avoid	
Exenatide ER	2 mg weekly	No dose adjustment	>50: No dose adjustment 30-50: Use with caution	Avoid	
Liraglutide	6 mg/mL	No dose adjustment	No dose adjustment	≥15: No dose adjustment	<15: Avoid
	3 mg	No dose adjustment	No dose adjustment	Avoid	
Lixisenatide	50 µg/mL; 100 µg/mL	No dose adjustment	No dose adjustment	Avoid	
Dulaglutide	0.75-1.5 mg weekly	No dose adjustment	No dose adjustment	≥15: No dose adjustment	<15: Avoid
Semaglutide	0.5-1.0 mg weekly	No dose adjustment	No dose adjustment	≥15: No dose adjustment	<15: Avoid
SGLT2 Inhibitors¶					
Dapagliflozin	5-10 mg OD	No dose adjustment	45-60: No dose adjustment <45: Not recommended	Avoid	
Canagliflozin	100-300 mg OD	No dose adjustment	45-60: 100 mg OD <45: Not recommended	Avoid	
Empagliflozin	10-25 mg OD	No dose adjustment		Avoid	
Ertugliflozin	5-15 mg OD	No dose adjustment	45-60: No initiation < 45: Not recommended	Avoid	
Luseogliflozin	2.5-5 mg OD	No dose adjustment	<60: Not recommended	Avoid	

Insulin
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.

Dose escalation will depend on tolerability and according to the PI.

*GFR in ml/min/1.73 m^2; *usual dose not maximum dose.*
^ Sulphonylureas should be used cautiously because of the increased risk of hypoglycaemia. First generation sulphonylureas (e.g. glibenclamide): generally, should be avoided due to long half-life and risk of hypoglycaemia in patients with CKD. Gliclazide and glipizide are the preferred agents among the second-generation sulphonylureas 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.
¶SGLT2-i – eGFR below which this class of agents can be prescibed is expected to change, with the advent of their significant reno-protective and cardio-protective benefits; however, the indication may be for their reno and cardio-protective benefits rather than specifically for glucose lowering. At lower eGFR, glucose-lowering efficacy of SGLT2-i are modest. Shown here are cut-offs based on individual agents' registered indication in Malaysia.

CKD: chronic kidney disease; OD: daily; BD: twice daily; TDS: three times daily; GFR: glomerular filtration rate; DPP4-i: Dipeptidyl peptidase-4 inhibitors; GLP1-RA: glucagon-like peptide-1 receptor agonists; SGLT2-i: sodium-glucose transport protein 2 inhibitors.

Adapted from Malaysian Society of Nephrology. Management of Chronic Kidney Disease (2nd ed); 2018[561] (Level III), Diabetes Canada 2018.[40] (Level III)

APPENDIX 8

CARDIOVASCULAR OUTCOMES TRIALS (CVOTS)

(A) DPP4-i

CVOTs DPP4-i	SAVOR-TIMI[193] (Level I)	EXAMINE[948] (Level I)	TECOS[191] (Level I)	CARMELINA[192] (Level I)	CAROLINA[160] (Level I)
Trial participants (n)	16,492	5,380	14,671	6,979	6,033
Intervention	Saxagliptin (QD)/ Placebo	Alogliptin (QD)/ Placebo	Sitagliptin (QD)/ Placebo	Linagliptin (QD)/ Placebo	Linagliptin (QD)/ Glimepiride
Main inclusion criteria	T2DM and history of or multiple risk factors for CVD	T2DM and ACS within 15-90 days before randomisation	T2DM and pre-existing CVD	T2DM and established CV and/or prevalent CKD	Early T2DM and pre-existing CVD or CV risk factors
Age (years)†	65.1	61.0	65.4	65.9	64.0
Diabetes duration (years)†	10.3	7.1	11.6	14.8	6.3
Median follow-up time (years)	2.1	1.5	3.0	2.2	6.3
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.7/4.6
Mean baseline HbA_{1c} (%)	8.0	8.0	7.2	8.0	7.2
Primary outcome	3-point MACE **1.00** (0.89-1.12) ***p<0.001 for non-inferiority***; *p=0.99 for superiority*	3-point MACE **0.96** (95% UL ≤1.16) ***p<0.001 for non-inferiority***; *p=0.32 for superiority*	4-point MACE **0.98** (0.89-1.08) ***p<0.001 for non-inferiority***; *p=0.65 for superiority*	3-point MACE **1.02** (0.89-1.17) ***p<0.001 for non-inferiority***; *p=0.74 for superiority*	3-point MACE **0.98** (0.84-1.14) ***p<0.001 for non-inferiority***; *p=0.76 for superiority*

CV death	1.03 (0.87-1.22)	0.79 (CI 0.60-1.04)	1.03 (0.89-1.19)	0.96 (0.81-1.14)	1.0 (0.81-1.24)
Non-fatal MI	0.95 (0.80-1.12)	1.08 (0.88-1.33)	0.95 (0.81-1.11) *(incl. fatal MI)*	1.12 (0.90-1.40)	1.01 (0.80-1.28)
Non-fatal stroke	1.11 (0.88-1.39)	0.91 (0.55-1.50)	0.97 (0.79-1.19) *(incl. fatal stroke)*	0.88 (CI 0.63-1.23)	0.88 (CI 0.63-1.23)
HF hospitalisation	1.27 (1.07-1.51) p=0.007	1.19 (0.90-1.58) p=0.22	1.00 (0.83-1.20) p=0.98	0.90 (0.74-1.08) p=0.26	1.21 (0.92-1.59)
All-cause mortality HR	1.11 (0.96-1.27)	0.88 (0.71-1.09)	1.01 (0.90-1.14)	0.98 (0.84-1.13) p=0.74	0.91 (0.78-1.06)
Worsening DKD	1.08[a] (0.88-1.32)	–	–	1.04[b] (0.89-1.22) **0.86**[c] (0.78-0.95) **p=0.003**	

† Age was reported as means in all trials except EXAMINE, which reported median; diabetes duration was reported as means in all trials except SAVOR- TIMI 53, EXAMINE and CAROLINA which reported medians.
[a] Doubling of serum creatinine, initiation of dialysis, renal transplantation, or creatinine >6mg/dL
[b] Sustained ESRD, death due to kidney failure, or sustained decrease of ≥40% in eGFR from baseline
[c] Albuminuria progression
Range in parenthesis indicates 95% Confidence Interval.

CVOTs: cardiovascular outcomes trials; DPP4-i: Dipeptidyl peptidase-4 inhibitors; CV: cardiovascular; CVD: cardiovascular disease; CHF: congestive heart failure; MI: myocardial infarction; HF: heart failure; HR: hazard ratio; DKD: diabetic kidney diseases; QD: once daily; T2DM: type 2 diabetes mellitus; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; MACE: major adverse cardiovascular events.

(B) SGLT2-i

CVOTs SGLT2-i	EMPA-REG[202] (Level I)	CANVAS program[201] (Level I)	DECLARE-TIMI[205] (Level I)	VERTIS CV*[952] (Level I)
Trial participants (n)	7,020	10,142 (4,330 & 5,812)	17,160	8,238
Intervention	Empagliflozin (QD)/ placebo	Canagliflozin (QD)/ placebo	Dapagliflozin (QD)/ placebo	Ertugliflozin (QD)/ placebo
Main inclusion criteria	T2DM and pre-existing CVD	T2DM and pre-existing CVD at ≥30 years of age or ≥2 CV risk factor at ≥50 years of age	T2DM and established ASCVD or multiple risk factors for ASCVD	T2DM and established ASCVD
Age (years)	63.1	63.3	63.9	64.4
Diabetes duration (years)	57% >10	13.5	11	13
Median follow-up time (years)	3.1	2.4	4.2	3.0
Prior CVD/ CHF (%)	99/**10.2**	65.6/14.4	40/10	100/23
Mean baseline HbA_{1c} (%)	8.1	8.2	8.3	8.2
Primary outcome	3-point MACE **0.86** (0.74-0.99) *p<0.001 for non-inferiority;* ***p=0.04 for superiority***	3-point MACE **0.86** (0.75-0.97) *p<0.001 for non-inferiority;* ***p=0.02 for superiority***	3-point MACE **0.93** (0.84-1.03) ***p<0.001 for non-inferiority;*** *p=0.17 for superiority* CV death or HF hospitalization **0.83** (0.73-0.95) ***p=0.005 for superiority***	3-point MACE **0.97** (0.85-1.11) *p<0.001 for non-inferiority*

CV death	0.62 (0.49-0.77) **p<0.001**	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.92 (0.77-1.11)
Non-fatal MI	0.87 (0.70-1.09)	0.85 (0.69-1.05)	0.89 (0.77-1.01)	1.04 (0.86-1.27)
Non-fatal stroke	**1.24** **(0.92-1.67)**	0.90 (0.71-1.15)	1.01 (0.84-1.21)	1.01 (0.84-1.21)
HF hospitalisation	0.65 (0.50-0.85) **p<0.001**	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.70 (0.54-0.90)
All-cause mortality HR	0.68 (0.57-0.82) p<0.001	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.93 (0.80-1.08)
Worsening DKD	0.61[a] (0.53-0.70) p<0.001	0.60[a] (0.47-0.77) 0.73[b] (0.67-0.79);	0.53[c] (0.43-0.66)	0.81[d] (0.64-1.04)

† Age was reported as means in all trials; diabetes duration was reported as mean in CANVAS and VERTIS CV; EMPA-REG reported as percentage of population with DM duration >10 yrs; DECLARE-TIMI 58, which reported median.
[a] Progression to macroalbuminuria, double of serum creatinine level, initiation of renal replacement therapy or death from renal disease
[b] ≥40% reduction in eGFR, renal-replacement therapy, or renal death
[c] ≥40% decrease in eGFR to <60 ml/min/1.73 m2, ESRD, or death from renal cause
[d] Doubling of serum creatinine, renal replacement therapy or death from renal causes
Range in parenthesis indicates 95% Confidence Interval.

**The hazard ratio for the primary outcome event is reported with a 95.6% confidence interval (adjusted to account for the interim analysis). The hazard ratio for key secondary outcome events are reported with a 95.8% confidence interval (adjusted to account for the interim analysis). The hazard ratios for other secondary outcome events are reported with a 95% confidence interval.*

CVOTs: cardiovascular outcomes trials; SGLT2-i: sodium-glucose cotransporter 2 inhibitors; CV: cardiovascular; CVD: cardiovascular disease; CHF: congestive heart failure; MI: myocardial infarction; HF: heart failure; HR: hazard ratio; DKD: diabetic kidney diseases; QD: once daily; T2DM: type 2 diabetes mellitus; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; MACE: major adverse cardiovascular events.

(C) GLP1-RA

CVOTs GLP1-RA	ELIXA[238] (Level I)	LEADER[230] (Level I)	SUSTAIN-6[259] (Level I)	EXSCEL[224] (Level I)	HARMONY outcomes[671] (Level I)	REWIND[248] (Level I)	PIONEER 6[670] (Level I)
Trial participants (n)	6,068	9,340	3,297	14,752	9,463	9,901	3,183
Intervention	Lixisenatide (QD)	Liraglutide (QD)	Semaglutide (OW)	Exenatide (QW)	Albiglutide (OW)	Dulaglutide (OW)	Semaglutide Oral (QD)
Main inclusion criteria	T2DM and history of ACS (<180 days)	T2DM and pre-existing CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	T2DM and pre-existing CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	T2DM with or without pre-existing CVD	T2DM with pre-existing CVD	T2DM and prior ASCVD event or risk factors for ASCVD	T2DM and pre-existing CVD, HF or moderate CKD at ≥50 years of age or CV risk at ≥60 years of age
Age (years)	60.3	64.3	64.6	62.0	64.1	66.2	66.0
Diabetes duration (years)	9.3	12.8	13.9	12.0	14.1	10.5	14.9
Median follow-up time (years)	2.1	3.8	2.1	3.2	1.6	5.4	1.4
Prior CVD/ CHF (%)	100/22.4	81.3/17.9	83/23.6	73.1/16.2	100/20	31.4/8.6	84.7/12.2
Mean baseline HbA_{1c} (%)	7.7	8.7	8.7	8.0	8.7	7.3	8.2
Primary outcome	4-point MACE 1.02 (0.89-1.17) *p=0.81*	3-point MACE **0.87** (0.78-0.97) *p=0.01*	3-point MACE **0.74** (0.58-0.95) ***p<0.001 for noninferiority, p<0.02 for superiority***	3-point MACE **0.91** (0.83-1.00) *p=0.06*	3-point MACE **0.78** (0.68–0.90) *p=0.0006*	3-point MACE 0.88 (0.79-0.99) p=0.026	3-point MACE **0.79** (0.57-1.11) ***p<0.001 for noninferiority***, *p=0.17 for superiority*

CV death	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.73-1.05)	0.93 (0.73-1.19)	0·91 (0·78-1·06)	0.49 (0.27-0.92)
Non-fatal MI	1.03 (0.87-1.22)	0.88 (0.75-1.03)	0.74 (0.51-1.08)	0.95 (0.84-1.09)	0.75 (0.61-0.90)	0·96 (0·79-1·16)	1.18 (0.73-1.90)
Non-fatal stroke	1.12 (0.79-1.58)	0.89 (0.72-1.11)	0.61 (0.38-0.99)	0.86 (0.70-1.07)	0.86 (0.66-1.14)	0·76 (0·61-0·95)	0.74 (0.35-1.57)
HF hospitalisation	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0·85 (0·70-1·04) [Composite of CV death or hHF]	0·93 (0·77-1·12)	0.86 (0.48-1.55)
All-cause mortality HR	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.95 (0.79-1.16)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
Worsening DKD	0.81[a] (0.66-0.99)	0.78[b] (0.67-0.92)	0.64[c] (0.46-0.88)	0.85[d] (0.74-0.98)	Reported as AEs	0·85[e] (0·77-0·93)	Reported as AEs

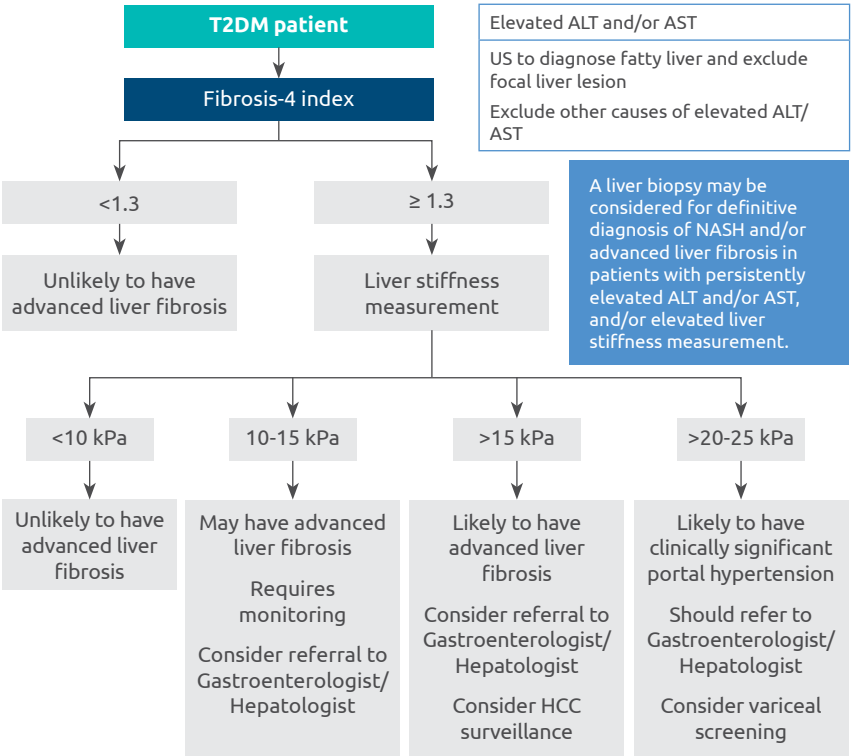
† Age was reported as means in all trials; diabetes duration was reported as means except EXSCEL, which reported median.
[a] New onset macroalbuminuria
[b] Nephropathy [defined as new onset macro-albuminuria or doubling of serum creatinine and eGFR ≤45 ml/min/1.73 m2, need for continuous renal-replacement therapy, or death from renal disease
[c] Persistent macroalbuminuria, persistent doubling of serum creatinine and creatinine clearance per MDRD <45ml/min/1.73m2, need for continuous renal-replacement therapy
[d] ≥40% decline in eGFR, renal replacement, renal death and new macroalbuminuria
[e] New macro-albuminuria, sustained decline in eGFR > 30% from baseline, or chronic renal replacement therapy
Range in parenthesis indicates 95% Confidence Interval.

CVOTs: cardiovascular outcomes trials; DPP4-i: Dipeptidyl peptidase-4 inhibitors; CV: cardiovascular; CVD: cardiovascular disease; CHF: congestive heart failure; MI: myocardial infarction; HF: heart failure; HR: hazard ratio; DKD: diabetic kidney diseases; QD: once daily; T2DM: type 2 diabetes mellitus; ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; MACE: major adverse cardiovascular events; MDRD: Modification of Diet in Renal Disease Study.

APPENDIX 9

FIBROSIS 4 INDEX

(A) Use of Fibrosis-4 index in assessment of NAFLD



T2DM: type 2 diabetes mellitus; kPa: kilopascals; HCC; hepatocellular carcinoma; US: ultrasound; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

(B) Calculating Fibrosis 4 index

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count } (\times 10^9/\text{L}) \times \text{ALT (U/L)}^{1/2}}$$

FIB-4	Interpretation
<1.3	Low risk for advanced fibrosis
≥1.3	Intermediate to high risk for advanced fibrosis

APPENDIX 10

ASSESSMENT OF SEXUAL DYSFUNCTION

(A) 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?		Very low	Low	Moderate	High	Very high
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No sexual activity	Never or almost never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse	Never or almost never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
	0	1	2	3	4	5
5. When you attempted intercourse, how often was it satisfactory for you?	Did not attempt intercourse	Never or almost never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
	0	1	2	3	4	5

All questions are pertaining to the last 4 weeks
Total up all scores (maximum score = 25)

Classification of the Severity of ED:

Total score	*Classification*
1-7	*Severe*
8-11	*Moderate*
12-16	*Mild-to-moderate*
17-21	*Mild*
22-25	*No abnormality*

(B) Sexual symptoms checklist for women

Sexual Symptom Checklist for Women

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function? Yes / No
   If No, please continue.
2. How long have you been dissatisfied with your sexual function? _____
3. Mark which of the following problems you are having, and tick the one that is most bothersome:
   - Little or no interest in sex
   - Decreased genital sensation (feeling)
   - Decreased vaginal lubrication (dryness)
   - Problem reaching orgasm
   - Pain during sex
   - Other: _____
4. Would you like to talk about it with your doctor? Yes / No

Adapted from Hatzichristou D et al. J Sex Med. 2010.[764 (Level III)]

APPENDIX 11

IDF-DAR RISK CATEGORIES FOR PATIENTS WITH T2DM WHO FAST DURING RAMADAN

Risk category	Patient characteristics	Comments
Category 1 Very high risk	1 or more of the following: 1. Severe hypoglycaemia within the 3 months prior to Ramadan 2. DKA within the 3 months prior to Ramadan 3. Hyperosmolar hyperglycaemic coma within the 3 months prior to Ramadan 4. History of recurrent hypoglycaemia 5. History of hypoglycaemia unawareness 6. Acute illness 7. Pregnancy in pre-existing diabetes, or GDM treated with insulin or SUs 8. Chronic dialysis or DKD stage 4 & 5 9. Advanced macrovascular complications 10. Old age with ill health	If patients insist on fasting then they should: √ Receive structured education √ Be followed by a qualified diabetes team √ Check their blood glucose regularly (SMBG) √ Adjust medication dose as per recommendations √ Be prepared to break the fast in case of hypo- or hyperglycaemia √ Be prepared to stop the fast in case of frequent hypo- or hyperglycaemia or worsening of other related medical conditions
Category 2 High risk	1 or more of the following: 1. T2DM with sustained poor glycaemic control* 2. Well-controlled T2DM on MDI or mixed insulin 3. Pregnant T2DM or GDM controlled by diet only or metformin 4. DKD stage 3 5. Stable macrovascular complications 6. Patients with comorbid conditions that present additional risk factors 7. People with diabetes performing intense physical labour 8. Treatment with drugs that may affect cognitive function	

Category 3 **Moderate/ low risk**	Well-controlled T2DM treated with one or more of the following: 1. Lifestyle therapy 2. Metformin 3. Acarbose 4. TZDs 5. Second-generation SUs 6. Incretin-based therapy 7. SGLT2-i 8. Basal insulin	Patients who fast should: √ Receive structured education √ Check their blood glucose regularly (SMBG) √ Adjust medication dose as per recommendations

DKA: diabetic ketoacidosis; GDM: gestational diabetes mellitus; SU: sulphonylurea; DKD: diabetic kidney disease; T2DM: type 2 diabetes mellitus; MDI: mixed dose insulin; TZD: thiazolidinediones; SGLT2-i: sodium-glucose transport protein 2 inhibitors; SMBG: self-monitoring blood glucose.

Adapted from the International Diabetes Federation–Diabetes and Ramadan International Alliance. Diabetes and Ramadan: Practical Guidelines. 2016.

APPENDIX 12

ASSESSMENT AND TREATMENT OF TOBACCO USE DISORDER

ASSESSMENT AND TREATMENT	
1.	Ask and document smoking status for all patients.
2.	Provide brief advice on quit smoking at every visit to all smokers.
3.	Assess level of nicotine addiction using Modified Fagerström Test for Cigarette Dependence Questionnaire **(COMPULSORY)** and verify smoking status using carbon monoxide (CO) breath analyser **(IF AVAILABLE)**.
4.	Offer pharmacotherapy to **all smokers** who are attempting to quit, unless contraindicated.
5.	If selected, use nicotine replacement therapy (NRT) for at least eight to twelve weeks, whereas varenicline should be used for at least twelve weeks.
6.	Combination therapy (e.g. two NRTs, a non-NRT, e.g. bupropion with an NRT) is better than monotherapy in smoking cessation treatment and may be most useful for those smokers at highest risk of relapse.
7.	Use smoking cessation medications with caution in special populations (e.g. children and adolescents, pregnant, breastfeeding women, psychiatric and substance abuse disorder patients).
8.	Arrange a minimum of six to eight face to face follow-up sessions for smoking cessation interventions in six months through counselling support team (health education officer, pharmacists or any officer trained for quit smoking services).

ABBREVIATIONS

ABG	Arterial blood gas
ACCORD	Action to Control Cardiovascular Risk in Diabetes Study
ACE	Angiotensin converting enzyme
ADI	Adequate dietary intake
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Study
AGIs	Alpha-glucosidase inhibitors
AHA	American Heart Association
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
BD	Twice daily
BMI	Body mass index
BP	Blood pressure
BUSE	Blood urea and serum electrolytes
CABG	Coronary artery bypass graft
CAN	Cardiovascular autonomic neuropathy
CARMELINA	Cardiovascular and Renal Microvascular Outcome Study With Linagliptin
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes

CCB	Calcium channel blockers
CCF	Congestive cardiac failure
CCM	Chronic care management
CGM	Continuous glucose monitoring
CHD	Coronary heart disease
CHO	Carbohydrate
CI	Confidence interval
CKD-EPI	CKD-epidemiology
CPG	Clinical Practice Guidelines
Cr-51-EDTA	Chromium-51-EDTA
CSF	Cerebrospinal fluid
CSII	Continuous SC insulin infusion
CV	Cardiovascular
CVD	Cardiovascular disease
CVOTs	Cardiovascular Outcome Trials
CXR	Chest x-ray
DAN	Diabetic autonomic neuropathy
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease
DPN	Diabetic peripheral neuropathies
DSPN	Distal symmetric polyneuropathy
ECG	Electrocardiogram
ED	Erectile dysfunction
eDKA	Euglycaemic diabetic ketoacidosis

eGFR	Estimated glomerular filtration rate
EMPA-REG	(Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
en	energy
ER	Extended release
ESKD	End stage kidney disease
FBC	Full blood count
FDC	Fixed dose combination
FPG	Fasting plasma glucose
FRS	Framingham Risk Score
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLD	Glucose lowering drug
GLP-1	Glucagon-like peptide-1
GLP1-RA	Glucagon-like peptide-1 receptor agonist
HbA_{1c}	Glycosylated haemoglobin
HDU	High dependency unit
HR	Hazard ratio
ICU	Intensive care unit
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IM	Intramuscular
IR	Immediate release
IV	Intravenous
kg	Kilogram
KUB	Kidney-ureter-bladder
LDL-C	Low density lipoprotein cholesterol

LOPS	Loss of protective sensation
MACE	Major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MNT	Medical nutrition therapy
MoH	Ministry of Health
MRP	Meal replacement powder
NAFLD	Non-alcoholic fatty liver disease
NDR	National Diabetes Registry
NGSP	National Glycohemoglobin Standardization Program
NPDR	Non-proliferative diabetic retinopathy
NSAIDs	Non-steroidal anti-inflammatory drugs
NSTEMI	Non-ST elevated myocardial infarction
OD	Daily
OGLD	Oral glucose lowering drug
OGTT	Oral glucose tolerance test
OM	On morning
ONS	Oral nutritional supplements
OR	Odd Ratio
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
PCI	Percutaneous intervention
POC	Point of care
PPG	Post-prandial glucose
QoL	Quality of life
RAS	Renin-angiotensin system

RCT	Randomised control trial
RPG	Random plasma glucose
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SC	Subcutaneous
SCORE	Systematic COronary Risk Evaluation
SE	Standard error
SGLT2-i	Sodium–glucose cotransporter 2 inhibitor
SMBG	Self-monitoring blood glucose
SR	Slow release
SSB	Sugar sweetened beverages
SSI	Sliding scale insulin
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

TDS	Three times daily
TG	Triglycerides
TOSCA IT	Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents Intervention Trial
TZD	Thiazolidinediones
UACR	Urine albumin-to-creatinine ratio
UKPDS	United Kingdom Prospective Diabetes Study
US	Ultrasound
UTI	Urinary tract infection
VEGF	Vascular endothelial growth factor
VLCD	Very low calorie diet
VRIII	Variable Rate Intravenous Insulin infusion

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Note: References 949-957 were added into the completed CPG as latest evidence published.