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CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION

SPECIAL EDITION

in Commemoration of the 18th Asean Federation of Endocrine Societies (AFES) Congress 2015

MALAYSIAN ENDOCRINE & METABOLIC SOCIETY

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

DIABETES MALAYSIA

FAMILY MEDICINE SPECIALISTS ASSOCIATION OF MALAYSIA

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS
(5th Edition)

This is a revised and updated Clinical Practice Guidelines (CPG) on Management of Type 2 Diabetes Mellitus.
This CPG supersedes the previous Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus (4th ed.) 2009.

STATEMENT OF INTENT

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

REVIEW OF THE GUIDELINE

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

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Electronic version is available on the following websites:
http://www.acadmed.org.my
http://www.diabetes.org.my
http://www.endocrine.my
http://www.mems.org.my
http://www.moh.gov.my

FOREWORD

Type 2 Diabetes Mellitus (T2DM) remains a major non-communicable disease in Malaysia. This is obviously due to poor lifestyle and made worse by co-existing medical problems including obesity. One of the main issues in the management is screening of the disease at an early stage in order to prevent complications and treat them early.

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

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

Thank you.

Datuk Dr. Noor Hisham Abdullah
Director General of Health
Ministry of Health, Malaysia

PREFACE

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

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

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

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

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

Prof. Dr. Nor Azmi Kamaruddin
Chairperson
Clinical Practice Guidelines Development Group

GUIDELINE DEVELOPMENT AND OBJECTIVES

Guideline Development

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

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

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

Reference was also made to other guidelines on the management of T2DM including American Diabetes Association (ADA) Standards of Medical Care in Diabetes, 2015; American Association of Clinical Endocrinologists' Comprehensive Diabetes Management Algorithm 2013; International Diabetes Federation (IDF) Global Guideline for Type 2 Diabetes, 2012; Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD); Diabetes in Adults Quality Standard, National Institute For Health and Care Excellence, 2011; Malaysian CPG on Management of Obesity 2004; Canadian Diabetes Association, Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada 2013; General Practice Management of Type 2 Diabetes, The Royal Australian College of General Practitioners and Diabetes Australia, 2014; Medical Nutrition Therapy Guidelines for Type 2 Diabetes. Malaysian Dietitians' Association, 2013; Trafford NHS Healthcare Trust: The Management Of Diabetic Ketoacidosis In Adults, 2012; Joint British Diabetes Societies Inpatient Care Group: The management of hyperglycaemic hyperosmolar state in adults with diabetes, 2012.

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

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

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

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

Objectives

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

Clinical Questions

The main clinical questions of this guideline are:

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

New Contents

The following are new additions to the CPG:

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

Target Population

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

Target Groups

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

THE MAIN CLINICAL INDICATOR FOR QUALITY MANAGEMENT

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

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

In Memory of Dr. Azura Dina Muhayidin
(1978-2015)
Al-Fatihah

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TABLE OF CONTENT

SECTION 1 TYPE 2 DIABETES MELLITUS: THE DISEASE

Background

- Type 2 Diabetes Mellitus (T2DM) is a prevalent non-communicable disease (NCD) which is increasing all over the world.
- It is manifested by a chronic hyperglycaemic state in conjunction with other metabolic derangements.
- T2DM is primarily due to insulin resistance as well as deficiency. The insulin resistance state results in increased hepatic glucose output, reduced utilisation of glucose by various organs, increased renal reabsorption of glucose and reduced incretin hormones production among others.
- In general T2DM is an important risk factor for cardiovascular disease and results in various other complications namely nephropathy, retinopathy, neuropathy and dermatopathy.
- Currently there is no known cure but the disease can be controlled enabling the individual to have an improved quality of life.
- The main aim of management is directed at reducing acute and chronic complications (microvascular and macrovascular).

Prevalence and the State of T2DM

- The National Health and Morbidity Survey (NHMS) 2011 reported diabetes prevalence figures of 15.2% and 20.8% for adults above the age of 18 and 30 years, respectively, in Malaysia. [1 (Level II-2)]
- Among adults above the age of 18 years old, the prevalence was highest in the Indians (24.9%) followed by Malays (16.9%) and Chinese (13.8%). [1 (Level II-2)]
- Of concern, 52% of those with diabetes above the age of 18 years old were unaware of their diagnosis. The percentage of undiagnosed diabetes is highest among the Malays (53%) followed by the Chinese (49%) and the Indians (42%). Similarly the proportion of undiagnosed diabetes is also highest in the young. [1 (Level II-2)]
- The prevalence of T2DM is increasing in the young with 2% and 4.9% of those between ages 18-19 years and 20-24 years, respectively, affected by it. [1 (Level II-2)]
- In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycaemic targets. [2,3 (Level II-2)]
- Up to 21.4% of T2DM patients in primary care were on insulin compared to 65.4% in tertiary institutions. [2,3 (Level II-2)]

Symptoms of Diabetes

- Majority are asymptomatic.
- Common symptoms include increased thirst, polydipsia, polyuria, lethargy, weight loss, blurring of vision and increased risk of infection.

Complications

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

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

Management

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

- The need for oral medications or insulin therapy depends on the symptomatology, state of glycaemic control and the presence of any complications.

SECTION 2 SCREENING AND DIAGNOSIS

2.1 Objective

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

2.2 Strategy

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

2.3 Who Should Be Screened

2.3.1 Symptomatic individuals

- Any individual who has symptoms suggestive of diabetes (tiredness, lethargy, polyuria, polydipsia, polyphagia, weight loss, pruritus vulvae, balanitis) must be screened. [4 (Level III)]

2.3.2 Asymptomatic individuals

Testing should be considered in all adults who are overweight or obese (BMI ≥23 kg/m^2 or have a waist circumference ≥80 cm for women and ≥90 cm for men), **and** have one or more of the following additional risk factors for diabetes:

- First-degree relative with diabetes
- History of cardiovascular disease (CVD)
- Hypertension (BP ≥140/90 mm Hg or on therapy for hypertension)
- Impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) on previous testing
- High density lipoprotein (HDL) cholesterol <0.9 mmol/L or triglycerides (TG) >2.8 mmol/L
- Other clinical conditions associated with insulin resistance (e.g. severe obesity and acanthosis nigricans)
- Women who delivered a baby weighing ≥4 kg or were diagnosed with gestational diabetes mellitus (GDM)
- Women with polycystic ovarian syndrome (PCOS)
- Physical inactivity
- Special populations (those who are receiving antiretroviral therapy [5 (Level II-1)] or atypical antipsychotic drugs [6 (Level II-2)])

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

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

2.4 Screening Test

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

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

Using A1c as a Screening Test for Diabetes

A1c is formed by a non-enzymatic glycation of haemoglobin. It reflects the average blood glucose level over the past 3 months. [7 (Level I)] Measurement of glycated haemoglobin levels revealed that A1c assay showed the least variance in normal subjects compared to plasma glucose levels. [8 (Level II-2)] Although

OGTT is the "gold standard" for diagnosing diabetes, it is known to be poorly reproducible and is cumbersome to perform. [9 (Level II-2)] Using A1c level to diagnose diabetes is convenient since therapeutic decisions are also based on this value, regardless of the findings of the OGTT. [8-13 (Level II-2-3)]

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

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

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

A1c is not appropriate for diagnosis of diabetes in:

1. Adolescents (<18 years old) since the diagnostic cut-off point was derived in those >18 years.
2. Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics.
3. Patients taking iron supplements (may falsely lower A1c levels).
4. Patients with acute pancreatic damage, including pancreatic surgery.
5. Presence of genetic, haematologic and illness-related factors that influence A1c and its measurement (e.g. haemoglobinopathies, rheumatoid arthritis, chronic liver disease, post-splenectomy).
6. Patients in chronic kidney disease (CKD) stage 4 or 5 and those on erythropoietin injections.
7. Anaemia due to iron, B12 or erythropoietin deficiencies.

A1c Reporting and the New SI Units

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

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

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

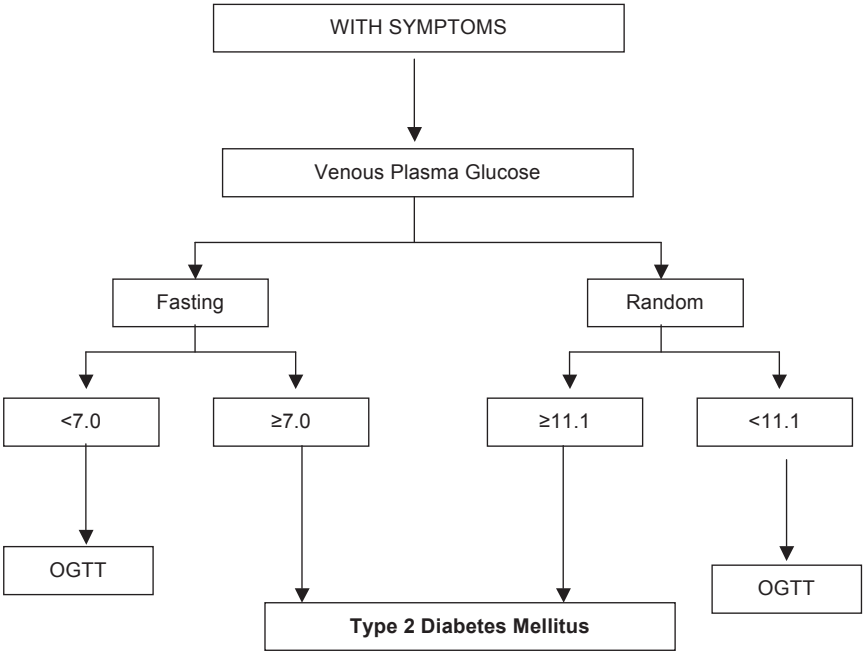
Table 1: Conversion Table for A1c Between NGSP and IFCC Values

NGSP-A1c (%)	IFCC-A1c (mmol/mol)
5.0	31
6.0	42
6.5	48
7.0	53
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

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

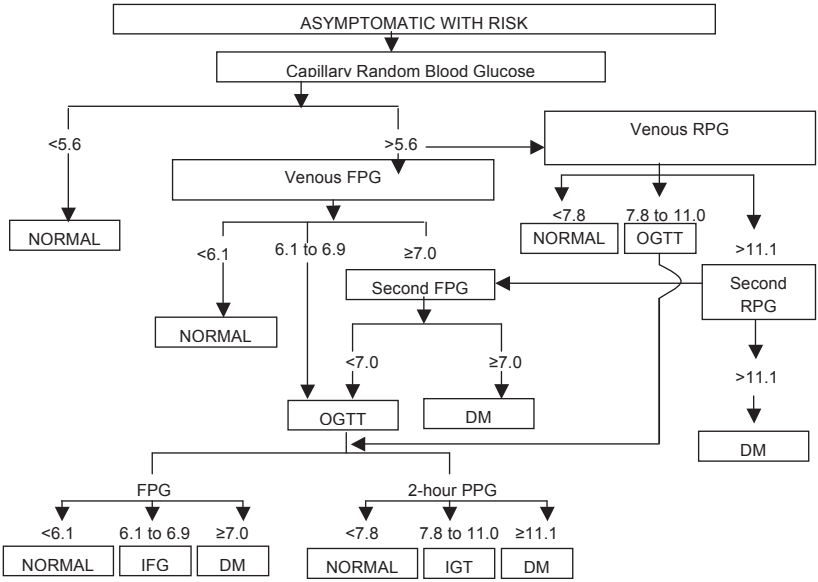
- Above NGSP-A1c level of 5%, every 1% increment is equivalent to 11 units (mmol/mol) in the IFCC-A1c.
- Conversion: A1c (mmol/mol) = [10.93 x A1c (%)] - 23.5

Algorithm 1: Screening for T2DM in Symptomatic Individuals



* All values are in mmol/L

Algorithm 2: Screening for T2DM in Asymptomatic Individuals



* All values are in mmol/L.

** FPG = fasting plasma glucose; RPG = random plasma glucose; OGTT = oral glucose tolerance test; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; DM = diabetes mellitus.

- If FPG ≥7.0 mmol/L or 2-hour PPG ≥11.1 mmol/L, a repeat glucose value (fasting or random) or A1c can be used to make the diagnosis of diabetes.

- For diagnosis of T2DM, venous plasma glucose value is required.

2.5 Schedule

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

2.6 Diagnosis

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

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

	Fasting	Random
Venous Plasma Glucose	≥7.0 mmol/L	≥11.1 mmol/L

- In symptomatic individual, one abnormal glucose value is diagnostic.
- In asymptomatic individual, 2 abnormal glucose values are required.

Table 3: Diagnostic Values for Glucose Intolerance and T2DM Based on OGTT [20] (Level III)

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
DM	≥7.0	≥11.1

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

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

	Normal	Pre-diabetes	Diabetes
A1c	<5.6% (38 mmol/mol)	5.6-6.2% (38-44 mmol/mol)	≥6.3% (45 mmol/mol)

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

2.7 Cardiovascular Risk Estimation

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

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

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

The above two CVD risk-stratifying tools have been validated in Malaysia using the NHMS II and III cohorts in adults aged between 40 and 65 years. [21] (Level II-2)

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

Recommendations: Screening and Diagnosis

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

SECTION 3 MANAGEMENT OF TYPE 2 DIABETES MELLITUS

3.1 Initial Assessment

At diagnosis, a detailed history, full physical examination (including fundoscopy and monofilament test) and baseline investigations must be done to assess the CVD risk factors and complications of diabetes.

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

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

Table 5: History Taking

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

Table 6: Physical Examination

Weight/waist	Body mass index (BMI) = weight (kg) / height^2 (m^2), waist circumference (WC)
Cardiovascular system	Blood pressure (lying and standing), neck and peripheral pulses, precordial examination
Eye	Visual acuity (with corrected vision), cataract, retinopathy (examine with pupils dilated)
Feet	Sensation, skin condition, pressure areas, interdigital lesions, and bone deformities
Peripheral nerves	Tendon reflexes Sensation: touch (e.g: with 10-g monofilament), vibration (e.g. with 128-Hz tuning fork)

Table 7: Investigations

Baseline	Fasting plasma glucose (FPG) A1c 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.

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

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

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

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

3.2 Diabetes Education

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

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

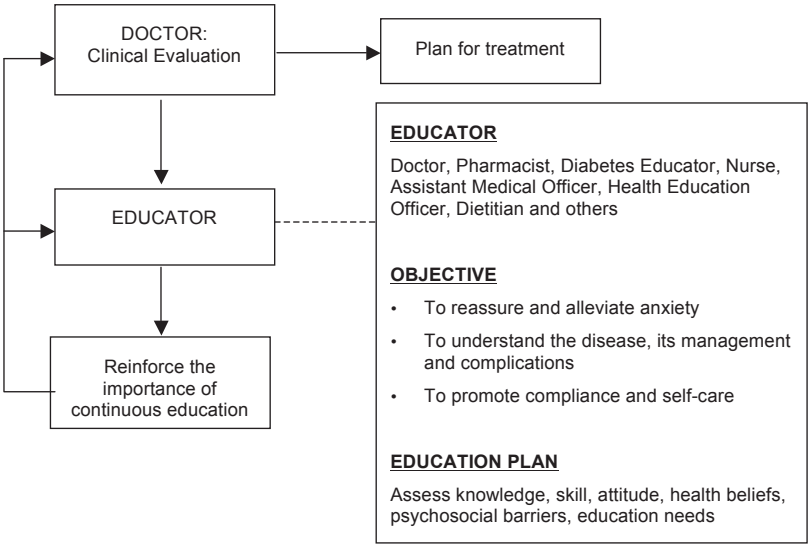
- A face-to-face delivery, cognitive reframing teaching method (a psychological technique that consists of identifying and then discussing the issues that impairs the person's ability to adjust to particular situations in this case the idea of having T2DM) and exercise content were more likely to improve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

- Periodic reinforcement of the diabetes education such as coaching via monthly telephone calls improves glycaemic control and compliance to complication screening. Interventions that encourage patient's active participation such as patient empowering group education and automatic telephone management program resulted in better outcomes. [31,32 (Level I), 33 (Level II-1)]

Table 8: Contents of Education: [20,22 (Level II-2), 34,35 (Level I), 36 (Level II-2), 37,38 (Level III)]

Contents / Scope of Education	
• Diet • Food exchanges • Exercise • Medication • Complications (acute and chronic) • Self-care/SMBG/foot care	• Stop smoking • 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

Algorithm 3: Education Strategies



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

3.3 Team Approach

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

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

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

Primary Care Practitioner

Primary care practitioner plays a central role in coordinating management of person with diabetes and in providing patient education as well as counseling. Primary care practitioner is the first point of contact with people with diabetes and usually assumes the responsibility for their overall management.

In some instances where the diabetes educator or dietitian is not available, primary care practitioner or the paramedics must undertake the responsibility to give detailed education to the patient.

Diabetes Educator

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

Dietitian

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

Physician/Endocrinologist/Diabetologist

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

Pharmacist

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

Ophthalmologist/Optometrist

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

Oral Health Professional

Dental and periodontal problems are common in patients with diabetes. They tend to have poorer oral hygiene and more severe gingival and periodontal diseases. [39 (Level II-2)] These may contribute to worsening of glycaemic control. [40 (Level III)] Patients with diabetes should be advised to see a dentist regularly.

Recommendations: Diabetes Education

1. All patients should be given diabetes education. *[Grade A]*
2. The type of education, content, duration and revision frequencies should depend on the need of the patients and the resources at the health care centre. *[Grade C]*
3. All newly diagnosed T2DM need to be reviewed by a medical doctor in which screening for other cardiovascular risks need to be carried out. *[Grade C]*
4. The significance of the legacy effects and metabolic memory should be emphasised to all newly diagnosed diabetic patients. *[Grade A]*

3.4 Targets for Control

Table 9: Targets for Control of Type 2 Diabetes Mellitus

Parameters		Levels
Glycaemic control*	Fasting or pre-prandial	4.4–7.0 mmol/L
	Post-prandial**	4.4–8.5 mmol/L
	A1c[++]	≤6.5%
Lipids	Triglycerides	≤1.7 mmol/L
	HDL-cholesterol	>1.0 mmol/L (male) >1.2 mmol/L (female)
	LDL-cholesterol	≤2.6 mmol/L[#]
Blood pressure [41-43 (Level I)]		≤135/75 mm Hg[§]
Exercise		150 minutes/week
Body weight [44,45 (Level I)]	If overweight or obese, aim for 5-10% weight loss in 6 months	

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

** Measured at least 90 minutes after meals.

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

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

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

Table 10: A1c Targets

Individualised A1c Targets and Patients' Profile		
Tight (6.0–6.5%)	**6.6–7.0%**	**Less tight (7.1–8.0%)**
• Newly diagnosed • Younger age • Healthier (long life expectancy, no CVD complications) • Low risk of hypoglycaemia	• All others	• Comorbidities (coronary disease, heart failure, renal failure, liver dysfunction) • Short life expectancy • Prone to hypoglycaemia

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

3.5 Lifestyle Modification

3.5.1 Medical Nutrition Therapy

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

The goals of MNT together with medication are to attain and maintain blood glucose, blood pressure and

lipid profile as close to normal as safely as possible. These goals can be achieved through healthy food choices.

General Recommendations

- Nutrition care by a dietitian should be provided under the following conditions: at diagnosis, sub-optimal metabolic and/or weight control, at initiation of insulin therapy, development of other comorbidities such as hyperlipidaemia, hypertension and chronic kidney disease. [51] (Level I)
- Diet counseling is effective to help lower A1c by an average of 1–2%. [52] (Level I) Patients who have diabetes should receive individualised nutrition care from a dietitian to achieve treatment goals. [53] (Level I)
- Dietary counseling should be individualised according to nutritional needs, severity of disease, cultural preferences and willingness to change. [51] (Level III)

Specific Recommendations

- **Prevention of Diabetes:**
  a) Weight loss of 5-10% of initial body weight over a 6-month period is recommended for all overweight or obese patients who have or at risk for diabetes. [44,45] (Level I)
  This can be achieved by:
    i. A reduced calorie diet. Standard weight-loss diets reduce daily energy by 500–1,000 kcal to achieve an initial weight loss of 0.5–1.0 kg per week. [54] (Level I)
    ii. Physical activity of 150 minutes per week i.e. 30 minutes five days or more per week. [55] (Level I)
    iii. A combination of reduced calorie diet, physical activity and behaviour modification can provide greater initial weight loss. [55] (Level I)
    iv. Meal replacements (MRPs) can be used as part of a comprehensive meal plan for weight loss and weight maintenance. [56] (Level I)
  b) There is no ideal percentage of energy for carbohydrate, protein and fat for diabetes. A balanced diet consisting of 45–60% energy from carbohydrate, 15–20% energy from protein and 25–35% energy from fat are encouraged. [57] (Level III) These recommendations must be individualised based on weight, glycaemic and other metabolic goals, cultural preferences and individual lifestyle.
  c) A high dietary fibre diet is encouraged for the prevention of diabetes . A high fibre diet (20–30 g fibre/day) consisting of vegetables, fruits, legumes and whole grain cereals is encouraged. [58] (Level II-2)
  d) Whole grains should form 50% of the total grain intake as recommended by the Malaysian Dietary Guidelines, 2010. Higher consumption of whole grains can contribute to the prevention of T2DM. [58] (Level II-2)
  e) Limit consumption of sugar-sweetened beverages (SSB) to less than 2 servings a day or about 10% of total daily caloric intake for prevention of diabetes and weight gain. [59,60] (Level II-2)

- **Management of Diabetes**
  In addition to the above recommendations:
  a) Total carbohydrate (CHO) intake should be monitored in patients with T2DM. [61] (Level I)
    i. Total CHO intake can be monitored by using grams, exchange list, household or hand measures as long as it is practical for patients to comprehend and follow. Please refer to **APPENDIX 1** and **APPENDIX 2**.
    ii. CHO intake must be kept consistent on a day-to-day basis if patient is on diet therapy alone, oral anti-diabetic agents (OADs) or fixed insulin regime.
    iii. It is prudent to individualise the distribution of the total CHO exchanges allowed in a day into meals according to the patient's lifestyle.

iv. If patient is adjusting their meal-time insulin doses or on insulin pump (i.e. flexible insulin) consistency is not required. Insulin doses should be adjusted to match CHO intake. Self-monitoring of blood glucose is essential to adjust CHO intake and insulin dose.

v. A minimum of 130 g/day CHO should be provided to ensure adequate intake of fibre, vitamins, and minerals, as well as to prevent ketosis and to provide dietary palatability. [62] (Level I)

vi. Sucrose (e.g. table sugar) intake must be counted as part of the total carbohydrate intake. [63] (Level III) Excess sucrose intake contributes to calories and may cause weight gain. [64] (Level II-2)

vii. Non-nutritive sweeteners do not impact glycaemic level. [60,64] (Level II-2) Intake should not exceed acceptable daily intake (ADI) levels.

b) In patients with normal renal function, usual protein intake of 15–20% energy has minimal effect on glycaemic control. [65] (Level I) It is recommended to include lean sources of protein such as lean meat, fish, chicken/poultry without skin and soy protein. In patients with impaired renal function, protein restriction of 0.8–1.0 g/kg body weight/day may be recommended. [66] (Level I)

c) Patients with diabetes should limit total fat (25–35% energy intake), saturated fats (<7% energy intake), minimal trans fat (<1% energy intake) and dietary cholesterol (<200 mg/day) for prevention and treatment of cardiovascular disease. [53,67] (Level I)

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

ii. A healthy diet incorporating oats, nuts and legumes, green leafy vegetables and soy protein may be beneficial for cardiovascular health. [67] (Level I)

d) In normotensive and hypertensive patients, a reduced sodium intake (<2,000 mg sodium/day or 5 g of salt a day or 1 teaspoon) with a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure. [68] (Level I)

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

e) Patients with diabetes have the same vitamin and mineral requirements as the general population. There is no clear evidence of benefit from the use of antioxidant vitamins A, C, E, selenium, herbs and omega-3 fatty acids in diabetes management. [69-71] (Level I)

f) Patients with diabetes do not require special oral nutritional supplement beverages unless malnourished, have not been eating well for prolonged periods of time or used as meal replacements for weight loss. [53] (Level III)

3.5.2 Low Glycaemic Index Diet

- Monitoring total CHO intake remains a key strategy in achieving glycaemic control. [72] (Level I)
- Both the amount and type of carbohydrates in food do affect blood glucose levels. The type of CHO is best described using the Glycaemic Index (GI) concept.

a) Glycaemic index (GI) is a measure to classify type of CHO based on their effect on the blood glucose level. It is a ranking system that indicate how quickly CHO food raises blood glucose

level. Food with high GI value raises blood glucose more than food with medium or low GI. Please refer to **APPENDIX 3**.

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

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

3.5.3 Physical Activity

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

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

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

General Recommendations

- Individuals should exercise 5 days a week, preferably most days of the week and with no more than 2 consecutive days without physical activity. [34 (Level I)]

- For patients with T2DM, supervised exercise programs have been particularly effective in improving glycaemic control, reducing the need for OADs and insulin, and producing modest but sustained weight loss. [78,79 (Level I)]

- Both aerobic and resistance exercise are beneficial for patients with diabetes, and it is optimal to do both types of exercise. The duration of exercise should be at least 150 minutes/week of moderate-intensity aerobic physical activity and/or at least 90 minutes/week of vigorous aerobic [34 (Level I)] and at least two sessions per week of resistance exercise. Please refer to **APPENDIX 5** for examples of exercise.

- Overweight and obese individuals should gradually increase physical activity to 60–90 minutes per day for long term weight loss.

- Any increase in daily energy expenditure is beneficial e.g. gardening, walking up stairs, washing the car, or mopping the floor.

- In order to prevent hypoglycaemia, medication doses can be reduced or extra carbohydrate can be consumed before or during physical activity.

Recommendations: Physical Activity

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

3.6 Medications

3.6.1 Oral Anti-diabetic (OAD) Agents

a) Biguanides (Metformin)

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

Table 11: Metformin Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Metformin	500 mg	Initial dose 500 mg OD Usual dose 1500 mg OD	1000 mg TDS
Metformin SR	850 mg	Usual dose 850 mg BD	850 mg TDS
Metformin XR	500 mg / 750 mg	Initial dose 500 mg OD Usual dose 2000 mg OD	2000 mg OD

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

b) Sulphonylureas (SUs)

- SUs reduce plasma glucose by increasing insulin secretion with an average A1c reduction of 0.4-1.6%. [83 (Level I)]
- The major adverse effect is hypoglycaemia. The risk is higher in renal impairment, liver cirrhosis and the elderly.
- Weight gain in the range of 1.5–2.5 kg is common.

- Among the second generation SUs, gliclazide and glimepiride are preferred over other SUs as they cause less risk of hypoglycaemia and less weight gain. [84,85 (Level I), 86 (Level III)]
- Glibenclamide has been shown to be associated with significant risk of hypoglycaemia and WHO recommends against its use in those above 60 years of age. [87 (Level I)]
- SUs are highly protein bound. Administration of drugs that can displace them (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), anti-thyroid drugs, sulpha drugs, anticoagulants and α-blockers) can increase the risk of hypoglycaemia.
- SUs should be taken 30 minutes before meals and can be combined with other OAD agents to improve glucose control.

Table 12: SU Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Glibenclamide	5 mg	2.5 mg OD	10 mg BD
Gliclazide	80 mg	40 mg OM	160 mg BD
Gliclazide MR	60 mg	30 mg OM	120 mg OM
Glipizide	5 mg	2.5 mg OM	10 mg BD
Glimepiride	2 mg / 3 mg	1 mg OM	6 mg OM

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

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

c) Meglitinides

- These are short acting insulin secretagogues that bind to a different site within the SU receptor.
- It has a shorter half-life than SUs, and is rapidly absorbed from the gastrointestinal tract with peak levels 1-hour post administration and eliminated within 4–6 hours. [88 (Level I)]
- It should be taken within 10 minutes before main meals.
- It reduces A1c by 1.0–1.2%. [88 (Level I)]
- It can be added to other OAD(s) except SU.
- It is associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent.
- It is primarily used to control postprandial hyperglycaemia (PPG). [88 (Level I)]

Table 13: Meglitinides Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Repaglinide	0.5 mg / 1 mg / 2 mg	0.5 mg with main meals	4 mg with main meals (not exceeding 16 mg daily)
Nateglinide	120 mg	60 mg with main meals	120 mg with main meals (not exceeding 360 mg daily)

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

d) Alpha-Glucosidase Inhibitors (AGIs)

- AGIs e.g. acarbose reduces the rate of absorption of polysaccharides in the proximal small intestine by inhibiting α-glucosidase enzymes. They should be taken with main meals. [90 (Level I)]

- It lowers postprandial glucose without causing hypoglycaemia.
- It is less effective in lowering glycaemia than metformin or SU, reducing A1c by 0.5–0.8%. [90 (Level I)]
- It has synergistic effects when used with other OAD(s) and may be combined with insulin.
- The commonest side effects are bloating, abdominal discomfort, diarrhoea and flatulence. [90 (Level I)]

Table 14: AGIs Formulation and Dosage

Drug	Formulation	Minimum Dose	Maximum Dose
Acarbose	50 mg / 100 mg	Initial dose 50 mg OD Usual dose 50–100 mg during main meals	100 mg TDS

e) Thiazolidinediones (TZDs)

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

Table 15: TZD Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Rosiglitazone	4 mg / 8 mg	4 mg OD	8 mg OD
Pioglitazone	15 mg / 30 mg	15 mg OD	45 mg OD

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

NOTE: Incretin Effect

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

f) Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

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

Table 16: DPP-4 Inhibitors Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Sitagliptin	25 mg / 50 mg / 100 mg	25 mg OD	100 mg OD
Vildagliptin	50 mg	25 mg BD	50 mg BD
Saxagliptin	2.5 mg / 5 mg	2.5 mg OD	5 mg OD
Linagliptin	5 mg	5 mg OD	5 mg OD
Alogliptin	6.25 mg / 12.5 mg / 25 mg	6.25 mg OD	25 mg OD

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

g) Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors

- This class of drugs selectively inhibits SGLT2, a transporter in the proximal tubule, thus reducing glucose reabsorption leading to an increase in urinary glucose excretion. [116-119 (Level I)]
- It reduces A1c by 0.2% to 0.8%. [120 (Level I)]
- This is accompanied by weight loss (2.5 to 3.0 kg) [120 (Level I)] and modest blood pressure reduction together with lower risk of hypoglycaemia.
- It is not recommended for those on concomitant treatment with loop diuretic.
- Efficacy of SGLT2-i is dependent on renal function and it is not recommended in patients with moderate to severe renal impairment (e-GFR <60 mL/min/1.73 m^2)
- It can be combined with other OAD(s) to improve glucose control.
- SGLT2 inhibitor has been shown to increase glucagon level and combining it with DPP-4 inhibitor will compensate this.
- Side effects include significant increased of genitalia and urinary tract infection.
- The US FDA has issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture. [121 (Level III)]
- A few cases of euglycaemic diabetic ketoacidosis (DKA) had been reported in patients who were on SGLT2 inhibitors and caution should be exercised when prescribing these agents in those with severe beta-cell insufficiency, latent autoimmune diabetes and in postsurgical patients. [122 (Level III)]
- The EMPA-REG clinical trial conducted in patients with T2DM at high risk for cardiovascular events showed a lower rate of cardiovascular events and all-cause mortality. [123 (Level I)] The reasons behind these findings are yet to be determined.

Table 17: SGLT2 Inhibitors Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Dapagliflozin	5 mg / 10 mg	5 mg OD	10 mg OD
Canagliflozin	100 mg / 300 mg	100 mg OD	300 mg OD
Empagliflozin	10 mg / 25 mg	10 mg OD	25 mg OD

3.6.2 Injectable Agents

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists [124 (Level I)]

Exenatide

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

Liraglutide

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

Lixisenatide

- Lixisenatide is given subcutaneously, once a day at any time of the day but at the same time every day.
- Lixisenatide can be used in combination with OADs and/or basal insulin. [144,145 (Level I)] Monotherapy with lixisenatide results in A1c reduction of 0.5-0.7%.
- Nausea, vomiting, diarrhoea and headache are common.

Caution:

- GLP-1 RA is not a substitute for insulin.
- GLP-1 RA should not be used in patients with a history of pancreatitis.
- GLP-1 RA should not be used if e-GFR <30 mL/min/1.73 m^2 (exenatide and lixisenatide) and e-GFR <60 mL/min/1.73 m^2 (liraglutide).

Table 18: GLP-1 RA Formulations and Dosage

Drugs	Formulation	Minimum Dose	Maximum Dose
Exenatide IR	5 µg/20 µL 10 µg/40 µL	5 µg BD	10 µg BD
Exenatide XR	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

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

3.6.3 General Guidelines for Use of Oral Anti-diabetic Agents

- OAD can be used as monotherapy or in combination with other OAD(s), and/or injectable agents (e.g insulin, GLP-1 receptor agonist).
- Agents that are known to improve fasting hyperglycaemia include metformin and TZDs while others reduce mainly postprandial hyperglycaemia.
- As first line therapy, metformin is the preferred choice. [146 (Level III)] Other OAD agents are acceptable alternatives.
- If glycaemic targets are not achieved, intensification of treatment should be made every 3 months. [4 (Level III)]
- If monotherapy fails, combination of other agents is recommended. [147 (Level III)]
- Compliance may be improved with daily dosing OAD agents.
- OAD agents are usually not the first line therapy in stress hyperglycaemia. Insulin therapy is recommended.
- Targets for control should be individualised.
- When indicated, start with a minimal dose of OAD agent, while re-emphasising diet and physical activity. This dose should be optimised gradually.

3.6.4 Combination of OADs, GLP-1 RA and Insulin

If targets have not been reached after optimal OAD therapy, consider adding:

- Pre-bed basal insulin, or
- Pre-dinner premixed insulin, or
- GLP-1 RA, as an alternative to intermediate or long-acting insulin with less incidence of hypoglycaemia and weight gain (provided the A1c is <10.0%)

Combining insulin with the following OADs has been shown to be effective in T2DM:

- Biguanide (metformin) [148-150 (Level I)]
- Insulin secretagogue (SU) [151 (Level I)]
- Insulin sensitizer (TZD) [152 (Level I)] (combination of a TZD and insulin is not generally recommended)
- Alpha-glucosidase inhibitor (AGI) [90,153 (Level I)]
- DPP-4 inhibitor [154-156 (Level I)]
- SGLT2 inhibitor [116-119 (Level I)]
- GLP-1 RA [124,142,144 (Level I)]

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

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

Recommendations: Combination of Anti-diabetic Agents

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

3.6.5 Initiation, Optimisation & Intensification of Insulin Therapy

(adapted from Practical Guideline to Insulin Therapy in Type 2 Diabetes Mellitus) [157 (Level III)]

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

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

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

Insulin therapy should be considered in the following situations:

- Inadequate glycaemic control on optimal dose and number of OADs [159 (Level I)] (refer **Algorithm 4**)

- As a short term use in the following:
  a) Acute illness or surgery
  b) Pregnancy
  c) Breast-feeding
  d) Severe metabolic decompensation (e.g. diabetic ketoacidosis, hyperosmolar hyperglycaemic state)
- As initial therapy in newly diagnosed T2DM
  a) Symptomatic (osmotic symptoms) regardless of A1c or FPG
  b) A1c >10% or FPG >13 mmol/L
  c) As part of early insulinisation treatment regime [160] (Level I), [161] (level II-2)

Insulin Types and Regimens

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

- **Prandial insulin** is administered pre-meal because of its short or rapid onset of action in controlling postprandial glucose excursion. It is also used in insulin pumps.
- **Basal insulin** is administered once or twice daily. The intermediate or long-acting pharmacokinetic profile covers the basal insulin requirements in between meals and night time.
- **Premixed insulin** is biphasic insulin that incorporates both the short or rapid-acting insulin with intermediate-acting insulin into a single preparation to cover for both postprandial glucose excursion as well as basal insulin needs

Table 19: Types of insulin and Their Pharmacokinetics Profiles

Insulin Preparation	Onset of Action	Peak Action (hours)	Duration of Action (hours)	Timing of Administration of Insulin
Prandial				
Short Acting, Regular Actrapid Humulin R Insuman R Insugen R	30–60 min	2–4	6–10	30 min before meal
Rapid 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 Humulin N Insuman N Insugen N	1–2 hour	4–8	8–12	Pre-breakfast / Pre-bed
Long Acting Analogue				
Glargine	30–60 min	Less peak	16–24	Same time everyday
Detemir	30–60 min	Less peak	16–24	
Degludec	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
Humulin 30/70	30 min	dual	16–18	
Novomix 30	10–20 min	1–4	16–20	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	
IDegAsp 30	10–20 min	1–4	24–40	5–15 min before meals

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

The long acting insulin analogue, which has less peak, results in lower hypoglycaemic episodes and reduced weight gain compared to conventional insulin. [162 (Level I)] At higher doses the long acting insulin analogue may have a significant peak. The rapid acting insulin analogues can be administered immediately before meals. Based on Cochrane reviews, insulin analogues are not superior to conventional human insulin in terms of efficacy other than reduced risk of symptomatic nocturnal hypoglycaemic events. [163,164 (Level I)]

Insulin Regimen

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

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

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

Insulin dose optimisation requires gradual, safe and prompt titration of insulin dose according to SMBG. [165 (Level I)] The insulin dose should be adjusted at least weekly to achieve glycaemic targets. Optimisation of the insulin dose should be an interactive process between the healthcare provider and the patient. This can be done at the diabetic resource centre, via telephone calls or text messages. It should be done within the first 3 months of starting insulin.

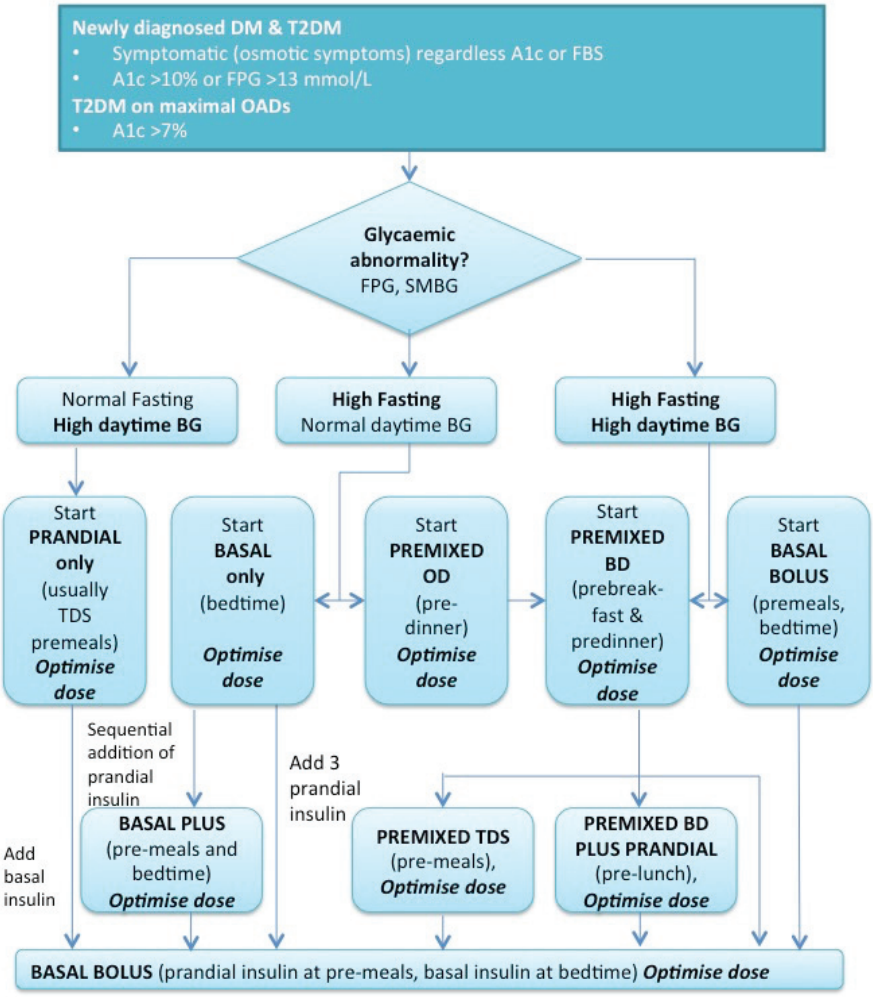
Often the insulin regimens started may need modification, which require switching to more intensive insulin regimens for better glycaemic control. This may entail increased number of injections. [159 (Level I)]

Insulin pump may be considered in patients who are still not controlled while on basal-bolus regime. [166 (Level I)]

Barriers to effective insulin therapy:

- There are numerous barriers to effective insulin therapy. These include patients and healthcare providers' factors.
- The biggest barrier is compliance and this should be adequately ascertained prior to any effort to intensify insulin therapy. [167 (Level II-3)]

Algorithm 4: Initiation and Optimisation of Insulin Therapy



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

Table 20: Insulin Regimen

No of injections per 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
2	BASAL	Intermediate acting (NPH) pre-breakfast and pre-dinner
	PREMIXED BD	Premixed insulin pre-breakfast and pre-dinner
	BASAL-PLUS 1	Basal insulin once daily + 1 prandial insulin
3	BASAL-PLUS 2	Basal insulin once daily + 2 prandial insulin
	PRANDIAL	Prandial insulin pre-breakfast, pre-lunch and pre-dinner
	PREMIXED TDS	Premixed pre-breakfast, pre-lunch and pre-dinner
	PREMIXED-PLUS 1	Premixed insulin pre-breakfast and pre-dinner + 1 prandial insulin pre-lunch
	PREMIXED-PLUS 2	Prandial insulin pre-breakfast and pre-lunch + premixed insulin pre-dinner
4	BASAL-BOLUS 1	Basal insulin once daily + prandial insulin pre-breakfast, pre-lunch and pre-dinner
5	BASAL-BOLUS 2	Intermediate acting (NPH) insulin pre-breakfast and pre-dinner + prandial insulin pre-breakfast, pre-lunch and pre-dinner

General Guidelines for Long Term Use of Insulin

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

Insulin Pump

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is another method to deliver insulin to diabetes patients. Insulin pump therapy is intended to closely mimic normal physiological insulin profile. Insulin pump therapy utilises only fast acting insulin and eliminates the use of long-acting insulin. It is safe and effective and can be initiated at any age. [168 (Level III)] A Cochrane review showed that insulin pump (without glucose sensor) gave slightly improved metabolic control over basal-bolus therapy. [169 (Level I)] In general, the combination of insulin pump and continuous glucose sensor resulted in improved control and less hypoglycaemia over basal bolus therapy alone. [170 (Level I)]

- **Indication for Insulin Pump Therapy:**

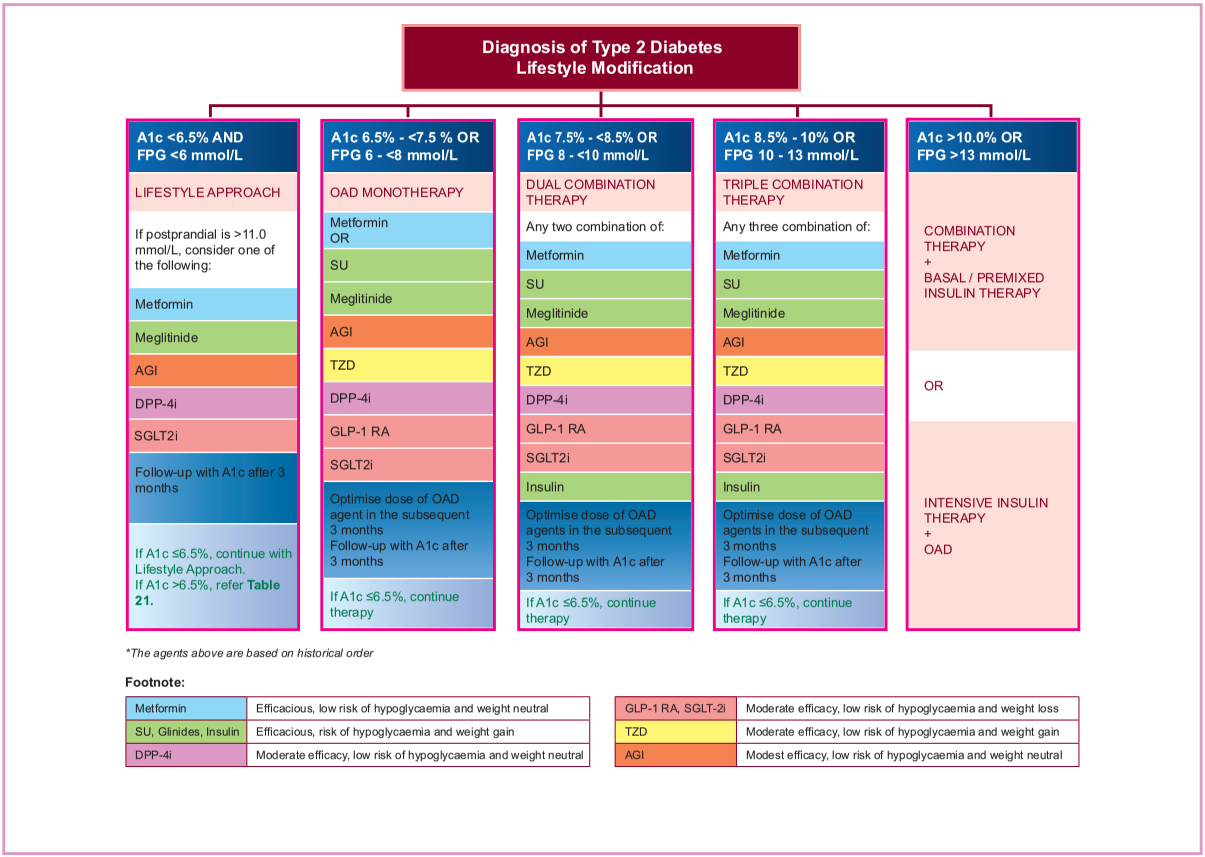
  a) Inadequate glycaemic control with MDI (multiple daily injections) therapy
  b) Recurrent severe hypoglycaemia
  c) Hypoglycaemia unawareness
  d) Dawn phenomenon
  e) Gastroparesis
  f) Frequent diabetic ketoacidosis

- **Patient's Pre-requisite for Insulin Pump Therapy**

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

Recommendations: Insulin Initiation, Optimisation and Intensification
1. The choice of insulin regimen should be individualised, based on the patient's glycaemic profile, dietary pattern and lifestyle. *[Grade C]*
2. The biggest barrier is compliance and this should be adequately ascertained prior to any effort to intensify insulin therapy. *[Grade C]*
3. Optimisation of insulin therapy should be done within the first 3 months of insulin initiation. *[Grade C]*

3.7.1 Algorithm 5: Treatment Algorithm for Newly Diagnosed T2DM



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

3.7.2 Table 21: Treatment Recommendations for Patients on Clinic Follow-up

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

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

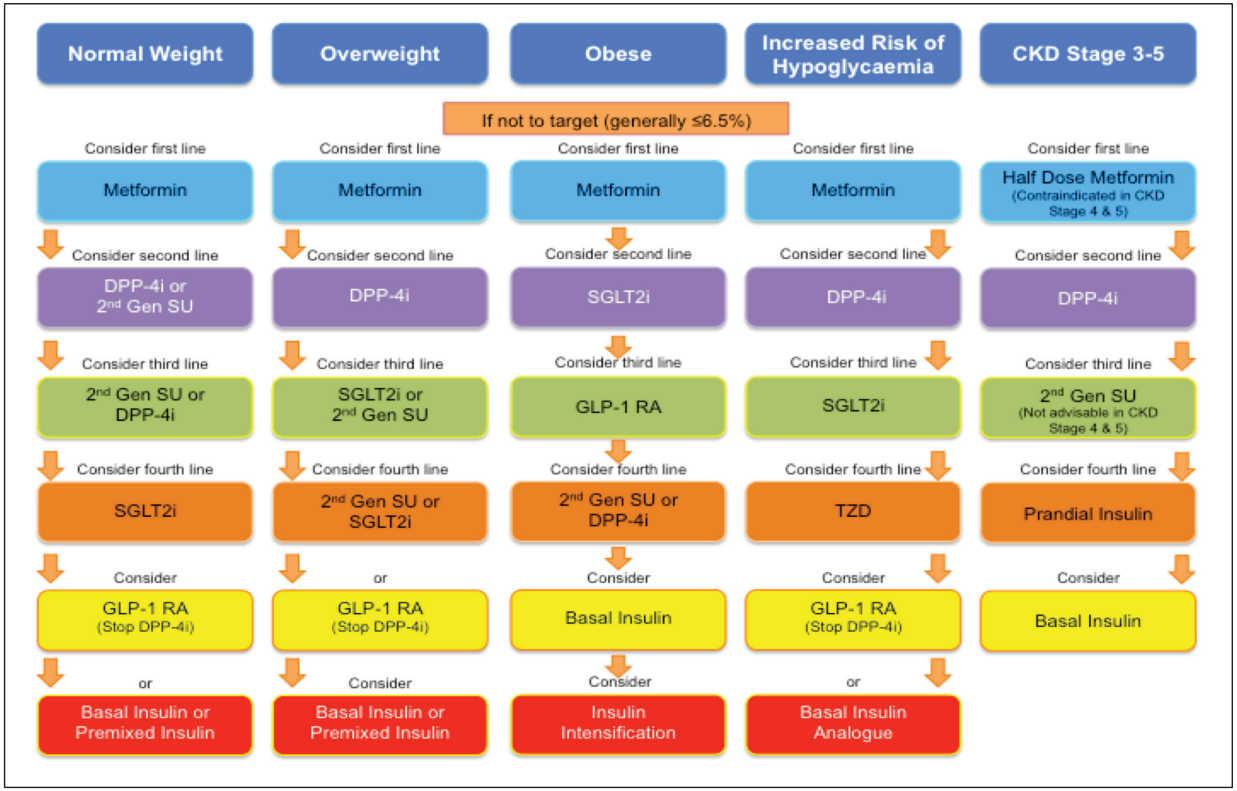
Box 1: Selection of Anti-diabetic Agents

SU	Efficacious, risk of hypoglycaemia, weight gain
Meglitinide	Efficacious, risk of hypoglycaemia, weight gain
AGI	Modest efficacy, low risk of hypoglycaemia, weight neutral
TZD	Efficacious, low risk of hypoglycaemia, weight gain
DPP-4i	Moderate efficacy, low risk of hypoglycaemia, weight neutral
GLP-1 RA	Moderate efficacy, low risk of hypoglycaemia, weight loss
SGLT2i	Moderate efficacy, low risk of hypoglycaemia, weight loss

Note:

1. If symptomatic (weight loss, polyuria, etc) at any A1c and FPG level, consider insulin therapy.
2. Glycaemic target should be individualised, however try to achieve as near normal glycaemia as possible without causing hypoglycaemia.

3.7.3 Algorithm 6: Suggested Treatment Approach for Specific Patient Profiles



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

Note:

1. Patients who are well-controlled on their existing drugs should continue with the treatment regime.
2. Bariatric surgery may be considered in patients with BMI ≥32 kg/m^2 and their diabetes cannot be controlled by lifestyle changes and pharmacotherapy.

3.7.4 Table 22: Efficacy of Various Anti-diabetic Agents

	MET	SU	GLN	AGI	TZD	DPP4-i	SGLT2-i	GLP-1 RA	Insulin
A1c reduction, %	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	FPG	Both	PPG	FPG	Both	Both	Both	Both
Hypoglycaemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
Congestive heart failure	↔	↔	↔	↔	↑	↔	↔	↔	↔
Cardiovascular disease	↓	↔?	↔	↔	↔	↔	↓?	↔	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
CKD	Avoid if GFR<30	Hypo-glycaemia	Hypo-glycaemia	↔	Fluid retention	Dose adjustment	Avoid if GFR<60	Avoid if GFR<30	Hypo-glycaemia
References	77 (Level I)	168,169 (Level I)	85 (Level I)	170 (Level I)	88-92 (Level I)	151-153 (Level I)	113-116 (Level I)	121 (Level I)	160,161,171, 172 (Level I)

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

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

Beneficial | Possible benefit | Neutral | Minimal risk | Increased risk

3.8 Monitoring

3.8.1 Glycated Haemoglobin (A1c)

Perform A1c approximately every 3–6 months (intervals depend on whether A1c targets are achieved):

- 3 monthly, if A1c is above target and to allow assessment of effect of therapeutic adjustment.
- 6 monthly, if A1c target is achieved and stable.

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

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

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

Limitations of A1c

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

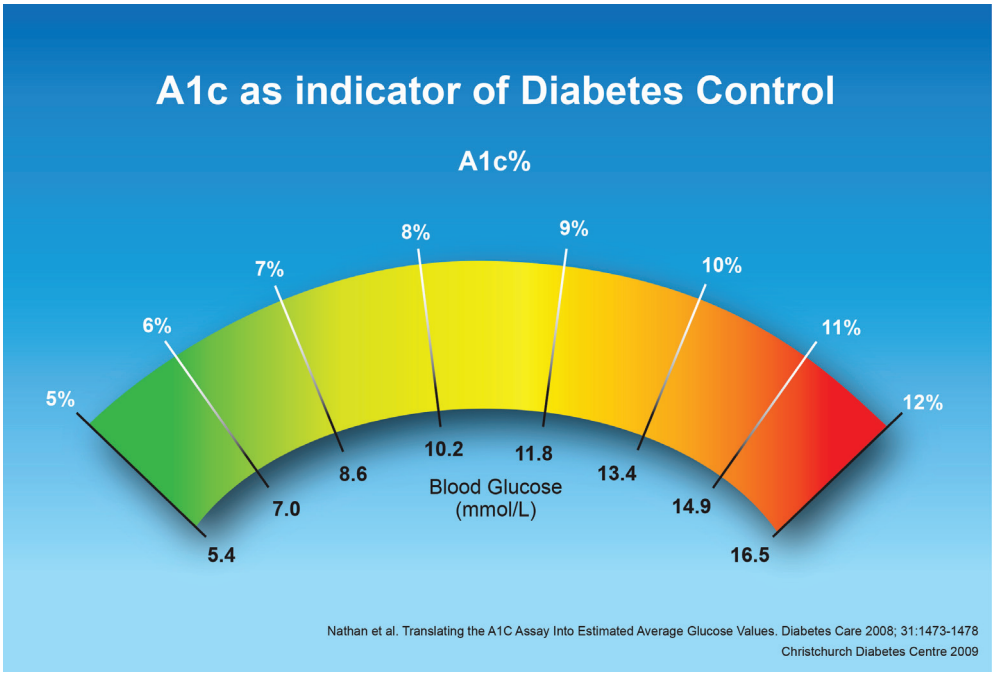


Figure 1: Correlation Between A1C Levels and Mean Glucose Levels [173 (Level II-2)]

Table 23: Mean Glucose Levels for Specified A1c Levels

A1c (%)	Plasma Glucose (mmol/L)			
	Mean	Fasting	Pre-meal	Post-meal
<6.5	7.0	6.8	6.6	8.0
<7.0	8.6	7.9	7.7	9.1
<7.5	-	8.4	8.4	9.8
<8.0	10.2	9.3	8.6	10.5
9.0	11.8	-	-	-
10.0	13.4	-	-	-
11.0	14.9	-	-	-
12.0	16.5	-	-	-

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

3.8.2 Fructosamine

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

3.8.3 Self-Monitoring of Blood Glucose (SMBG)

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

Frequency of blood glucose testing depends on the glucose status, glucose goals and mode of treatment.

Although SMBG has not been shown to have a significant impact on outcome measures such as A1c and body weight, it is recommended as part of a wider educational strategy to promote self-care.

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

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

Table 24: Recommendations for Self-Monitoring of Blood Glucose

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

Glucose Monitoring in Relation to Different Insulin Regime

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

OAD(s) + Bedtime Insulin

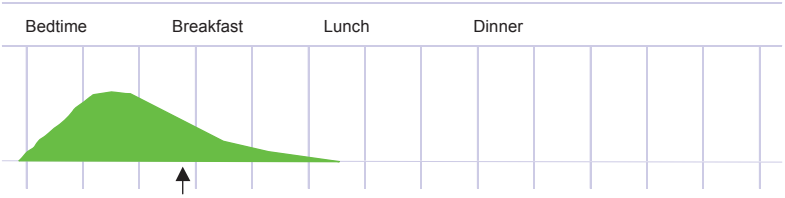


Figure 2: OAD(s) + Bedtime Insulin – Intermediate Acting Insulin

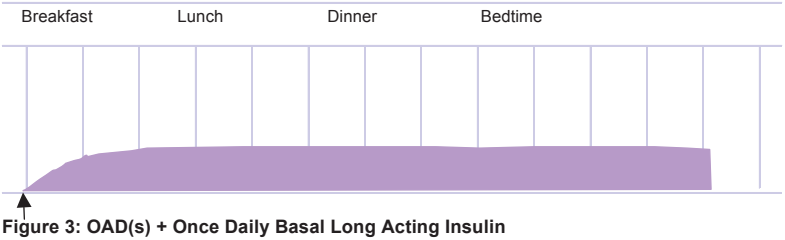


Figure 3: OAD(s) + Once Daily Basal Long Acting Insulin

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

Basal-Bolus Insulin Regimen

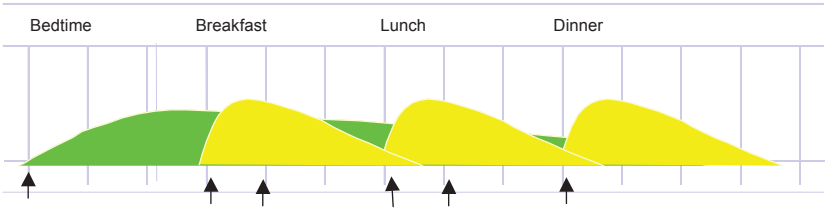


Figure 4: Basal-Bolus Insulin Regimen

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

Twice Daily Premixed or Combination Intermediate-Acting with Short-Acting Insulin

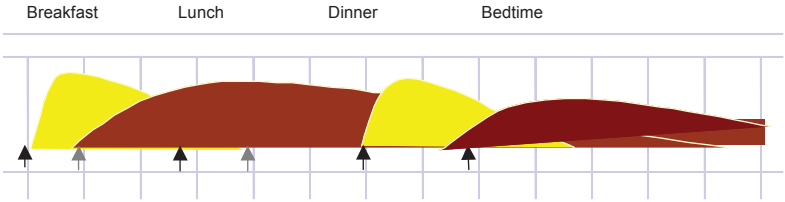


Figure 5: Intermediate-Acting with Short-Acting Insulin

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

▲ = Recommended timing of SMBG

3.8.4 Monitoring of Other Risk Factors

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

Table 25: Clinical Monitoring Schedule

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

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

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

√	Conduct test
+	Conduct test if abnormal on 1st visit or symptomatic
-	No test required

Recommendations: Monitoring

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

3.9 Management of Comorbidities in Type 2 Diabetes Mellitus

3.9.1 Hypertension and Diabetes

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

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

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

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

Management

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

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

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

- It is recommended that one or two antihypertensive medications should be administered at bedtime. There is evidence that taking at least one antihypertensive medication at bedtime reduce risk of CVD events. [185] (Level I)

Table 26: Choice of Antihypertensive Drugs in Diabetic Patients with Concomitant Conditions

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

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

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

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

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

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

Recommendations: Hypertension and Diabetes

1. Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >140 mm Hg systolic and/or >90 mm Hg diastolic *[Grade C]* and treat to goal SBP <135 mm Hg and goal DBP <75 mm Hg. *[Grade A]*
2. ARBs or ACEIs are the agents of choice for patients with diabetes and microalbuminuria or proteinuria. *[Grade A]*
3. In pregnant individuals with diabetes and hypertension, recommended BP target goals should be 110-129/65-79 mm Hg. *[Grade C]*

3.9.2 Hyperlipidaemia and Diabetes

DM is a coronary heart disease (CHD) risk equivalent. Control of hyperglycaemia in T2DM has not been associated with significant decrease in CVD events [43,47,188 (Level I)] except in overweight people with diabetes who were given metformin. [189 (Level I)] Thus, efforts must also be directed to control other risk factors such as dyslipidaemia, hypertension and other new emerging risk factors.

Screening

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

Primary target: LDL cholesterol

- In individuals without overt CVD
  a) All patients over the age of 40 should be treated with a statin regardless of baseline LDL cholesterol levels. [190,191 (Level I)]
  b) The target of LDL cholesterol level is 2.6 mmol/L.
  c) If the above target is unattainable, aim for a 50% reduction in pre-treatment LDL-C level. [192 (Level III)]
- In individuals with overt CVD
  a) All patients should be treated with a statin. [193 (Level III)]
  b) The target of LDL cholesterol level is 1.8 mmol/L. [191,194 (Level I)]
  c) If the above target is unattainable, aim for a 50% reduction in pre-treatment LDL-C level. [192 (Level III)]

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

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

In adolescents with T2DM, screening for lipid disorders should be done at diagnosis after glycaemic control is achieved. If normal lipid values are obtained, screening should be repeated every 2 years. [195-198 (Level III)]

Management

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; weight loss (if indicated) and increased physical activity have been shown to improve the lipid profile in patients with diabetes.

- Lowering LDL is the main aim of treatment.

- Any effort to increase HDL should be done together with the main purpose to reduce LDL. Using pharmacotherapy to increase HDL alone showed mixed result, with no or small benefit. [199 (Level III)]

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

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

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

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

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

- Statin therapy is contraindicated in pregnancy.

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

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

Table 27: Drug Therapy for Diabetic Dyslipidaemia

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

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

Recommendations: Diabetic Dyslipidaemia

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

3.9.3 Obesity and Diabetes

Based on the NDR report 2012, 83.4% of patients are either overweight or obese. [2 (Level II-3)] Many anti-diabetic agents are associated with weight gain, and attempts should be made to minimise these medications without compromising glycaemic control or to switch to alternative agents not associated with weight gain. **Table 28** showed the anti-diabetic agents and their effects on weight.

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

Weight Gain	Weight Neutral	Weight Reduction
Insulin TZDs Sulphonylureas Meglitinides	Metformin AGI DPP-4 inhibitors	GLP-1 RA SGLT2 Inhibitors

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

Table 29: Classification of Weight by BMI [212 (Level III)]

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

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, blood pressure, lipid profile and quality of life.
- The goals of therapy are to achieve optimal glycaemic and metabolic control, through lifestyle modifications including behavioural change, physical activity and dietary interventions.

Non-pharmacological interventions

- Dietary interventions (caloric restriction of 1200 to 1500 kcal/day). [213 (Level I)]
- Increased physical activity consisting of approximately 250 to 300 minutes per week of moderate-intensity exercise. This includes muscle strengthening and resistance exercises 2 to 3 times per week. [214 (Level III)]

Pharmacological Interventions

- Pharmacotherapy can be considered for diabetic patients with BMI ≥27.0 kg/m^2 after failing of 6 months of lifestyle modification. [212 (Level III)]

- Two anti-obesity agents have been approved, phentermine and orlistat for the management of obesity. [215,216 (Level I), 217 (Level II-3)] Phentermine is only indicated for short-term use and caution should be exercised in those with poorly-controlled blood pressure and coronary artery disease.

- GLP-1 RA when used as anti-diabetic agents is associated with significant weight loss (4.5 kg). [131] (Level I)

Table 30: Anti-obesity Agents Indicated for Use in Diabetes [218] (Level I)

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

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

Bariatric Surgery

- Bariatric surgery is recommended when lifestyle and pharmacological intervention have failed in the severely obese diabetic patients. [212] (Level III)

- The Asian Consensus Meeting on Metabolic Surgery (ACMOMS) recommends bariatric surgery for the following: [219] (Level III)
  a) Diabetic patients >32 kg/m^2
  b) Diabetic patients >30 kg/m^2 with 1 or more features of metabolic syndrome

- Evaluation should be performed by a multidisciplinary team consisting of endocrinologist, bariatric surgeon, psychiatrist, dietitian and physiotherapist prior to surgery.

- Criteria for bariatric surgery are shown in **Table 31**:

Table 31: Criteria for Bariatric Surgery

Factor	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 • Compliance to medical management • Continued dietary restriction
Exclusion criteria	• BMI <30 kg/m^2 • Current drug or alcohol abuse • Severe psychiatric illness • Lack of comprehension of the benefits, risks, expected outcomes and required lifestyle changes.

Choice of Procedures

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

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

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

Recommendations: Obesity and Diabetes

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

4.1 Hypoglycaemia

Definition

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

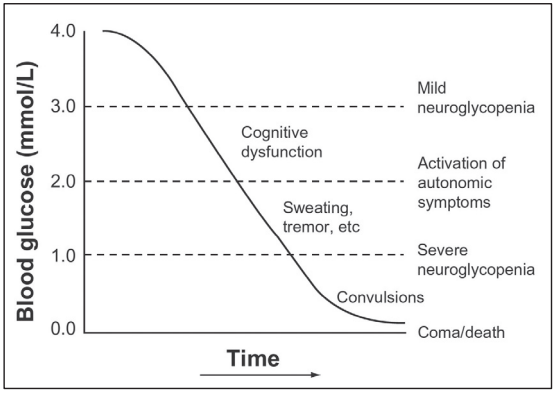
Table 32: Symptoms of Hypoglycaemia

Autonomic	Neuroglycopenic
• Trembling • Palpitations • Sweating • Anxiety • Hunger • Nausea • Tingling	• Difficulty concentrating • Confusion • Weakness • Drowsiness • Vision changes • Difficulty speaking • Headache • Dizziness

Table 33: Severity of Hypoglycaemia

Mild	Autonomic symptoms are present. The individual is able to self-treat.
Moderate	Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.
Severe	Individual requires assistance of another person. May become unconscious, plasma glucose is usually less than 2.8 mmol/L.

Figure 6: Hypoglycaemic Symptoms Based on Blood Glucose Levels



- Adapted from Kedia N. Treatment of severe diabetic hypoglycaemia with glucagon: an underutilized therapeutic approach. Diabetes, metabolic syndrome and obesity: targets and therapy, 2011. [224 (Level II-2)]

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

Treatment of Hypoglycaemia

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

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

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

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

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

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

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

Hypoglycaemia Unawareness

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

- Hypoglycaemia unawareness increases the incidence of severe hypoglycaemia by 17-fold for T2DM patients. [228 (Level III)]

- Hypoglycaemia unawareness should trigger re-evaluation of the treatment regimen. Patients with hypoglycaemia unawareness should be advised to increase their glycaemic targets to strictly avoid further hypoglycaemia for at least several weeks, to partially reverse hypoglycaemia unawareness and to reduce risk of future episodes.

Nocturnal hypoglycaemia

- The incidence of nocturnal hypoglycaemia events is difficult to measure because many events are asymptomatic, unrecognised and unreported, partly due to lack of self-monitoring at night time. [229] (Level III)
- In a study using continuous glucose monitoring (CGM) in T2DM, nearly three-fourth of all hypoglycaemic events occurred at night-time. [230] (Level II-2)
- This risk is higher especially in the elderly. In elderly diabetic, it was demonstrated that 69% experienced more than one nocturnal hypoglycaemic events, with an average duration of 56 minutes and none was recognised by the patients. [231] (Level II-3)
- Both physiologic and behavioural defences against hypoglycaemia have been shown to be further compromised during sleep. This explains the high frequency of nocturnal hypoglycaemia seen in diabetic patients. [232] (Level III)
- The clinical manifestations are vague, and may include: [233,234] (Level III)
  a) poor sleep quality
  b) vivid dreams or nightmares
  c) waking with chills or sweating
  d) morning headache
  e) chronic fatigue
  f) mood changes and
  g) nocturnal convulsions
- Undetected nocturnal hypoglycaemia can promote hypoglycaemia unawareness, blunt counterregulatory responses, create anxiety, reduce quality of life and increase treatment costs. [235] (Level II-3) It can also result in negative outcomes such as falls, accidents and arrhythmias.

Hypoglycaemia and Cardiovascular Disease

- Cardiovascular disease has been shown to be the most common cause of death (52%) in patients with T2DM. [236] (Level III)
- More recently, hypoglycaemia has also been shown to exert several CV effects [237,238] (Level III) and some studies have suggested a link between hypoglycaemic events and CVD in T2DM patients. [237,239] (Level III)
- Hypoglycaemia causes a cascade of physiological effects and may induce cardiac arrhythmias [240] (Level III) contributing to increase CVD risk and sudden cardiac death.
- During an acute hypoglycaemic episode, heart rate and systolic blood pressure increase, blood flow increases in the myocardium, cardiac output, stroke volume, and myocardial contractility increase, adding stress to the CV system.
- Hypoglycaemia can also induce changes in the conduction system of the heart, including prolonging the QTc interval [241,242] (Level III) lengthening repolarisation, and causing ST wave changes. [240] (Level III)

These cardiac rhythm disturbances may results in sudden cardiac death observed during hypoglycaemia.

- In three major trials (ACCORD, ADVANCE and VADT) [43,243,244 (Level I)] more episodes of hypoglycaemia were observed in the intensively treated arms. In particular, the ACCORD trial was associated with a significant increase in mortality.

- Several explanations were postulated to explain the findings in ACCORD, but the most obvious factor was hypoglycaemia, which was threefold higher in the intensive arm. [43 (Level I)] However, it remains unknown whether hypoglycaemia was the direct cause of increased mortality.

- In VADT, hypoglycaemia was found to be a strong predictor for cardiovascular mortality and admission for heart failure. [244 (Level I)]

Recommendations: Hypoglycaemia

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

4.2 Diabetic Ketoacidosis (DKA)

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

- It has a high mortality rate if unrecognised. The overall mortality is <1%, but a mortality rate >5% in the elderly has been reported. [245,246 (Level II-3)]

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

- Diagnostic criteria:
  All three must be met: [247 (Level III)]
  a) Capillary blood glucose >11 mmol/L
  b) Capillary ketones >3 mmol/L or urine ketones ≥2+
  c) Venous pH <7.3 and/or bicarbonate <15 mmol/L

- High-dependency unit (HDU) admission and insertion of central line may be required in the following circumstances:
  a) Elderly
  b) Pregnant ladies
  c) Heart or kidney failure
  d) Other serious comorbidities
  e) Severe DKA by following criteria:
     i. Venous bicarbonate <5 mmol/L
     ii. Blood ketones >6 mmol/L
     iii. Venous pH <7.1
     iv. Hypokalaemia on admission (<3.5 mmol/L)
     v. Glasgow Coma Scale (GCS) <12
     vi. Oxygen saturation <92% on air (arterial blood gases required)

vii. Systolic BP <90 mm Hg
viii. Pulse >100 or <60 beats/minute
ix. Anion gap >16 [Anion Gap = $(Na^+ + K^+) – (Cl^- + HCO3^-)$]

Algorithm 7: Principles of Management

1st Hour: Immediate Management

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

Step 2. Commence a fixed rate intravenous insulin infusion (IVII) (0.1 unit/kg/hr based on estimate of weight).

50 units short-acting human insulin made up to 50 mL with 0.9% saline solution.

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

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

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

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

Initial Fluid & Potassium Replacement

Restoration of circulating volume is a priority

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

- Give 500 mL of 0.9% saline solution over 10–15 minutes. If SBP remains <90 mm Hg, repeat.
- Most patients require between 500-1000 mL given rapidly. Consider colloids e.g. Gelafundin if BP fails to pick up.
- Once SBP >90 mm Hg give 1000 mL of 0.9% saline over the next 60 minutes.

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

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

Potassium replacement:

Potassium level (mmol/L)	Potassium replacement mmol/L of infusion solution
>5.5	Nil
3.5–5.5	40 mmol/L (3 g KCL)
<3.5	Additional potassium required

Caution:
Withold potassium replacement if no urine output.

Intravenous bicarbonate:
The use of intravenous bicarbonate is not indicated to correct acidosis in DKA due to:
- Rise in pCO_2 in CSF which may lead to a paradoxical increase in CSF acidosis.
- Delay in the fall of blood lactate and ketone level.
- Risk of cerebral oedema especially in younger age groups.

2nd - 6th Hour

Aims of treatment:

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

Step 7. Reassess patient, monitor vital signs

- Hourly blood glucose (lab blood glucose if meter reading 'HI')
- 4-6 hourly blood or urine ketones
- Venous blood gas for pH, bicarbonate and potassium at 60 minutes, followed by 4-6 hourly (depending on the severity of acidosis)
- If potassium is outside normal range, reassess potassium replacement and check 1-2-hourly depending on the severity

Step 8 Continue fluid replacement via infusion pump as follows:

- 1000 mL of 0.9% saline with potassium chloride over next 2 hours
- 1000 mL of 0.9% saline with potassium chloride over next 4 hours
- Once blood glucose falls below 14 mmol/L:
  - Switch to 5% dextrose at 125 mL/hr and reduce insulin infusion rate to 0.05 units/kg/hour; or
  - Switch to 10% dextrose at 125 mL/hr with no change in insulin infusion rate.

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

Step 9. Assess response to treatment

Insulin infusion rate may need review if:

- Blood ketones not falling by at least 0.5 mmol/L/hr
- Venous bicarbonate not rising by at least 3 mmol/L/hr
- Plasma glucose not falling by at least 3 mmol/L/hr
- Continue fixed rate IVII until ketones less than 0.3 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L

If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present.

If equipment is working but response to treatment inadequate, increase insulin infusion rate by 1 unit/hr increments hourly until targets achieved.

Additional measures

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

6th - 12th Hour

Aims:

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

Step 10 Reassess patient, monitor vital signs

- Continue IV fluid at reduced rate
- 1000 mL of 0.9% saline with potassium chloride over 4 hours (continuation from the 5th hour)
- 1000 mL of 0.9% saline with potassium chloride over 8 hours
- Once blood glucose falls below 14 mmol/L:
  - Switch to 5% dextrose at 125 mL/hr and reduce insulin infusion rate to 0.05 units/kg/hour; or
  - Switch to 10% dextrose at 125 mL/hr with no change in insulin infusion rate.

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

Step 11. Review biochemical and metabolic parameters

- At 6 hours check venous pH, bicarbonate, potassium, blood ketones and glucose
- Resolution is defined as:
  - Blood ketones <0.3 mmol/L,
  - Venous pH >7.3 (do not use bicarbonate as a surrogate at this stage)
- Ensure referral has been made to diabetes team

If DKA not resolved review insulin infusion (see **Step 9**)
If DKA resolved go to BOX entitled **Resolution of DKA**

12-24 hours

By 24 hours the ketonaemia and acidosis should have resolved.

Aim:

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

Step 12. Reassess patient, monitor vital signs, review biochemical and metabolic parameters

- At 12 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones <0.3 mmol/L, venous pH >7.3
- If not resolved review **Step 9** and **Step 10**.

If DKA resolved go below

Resolution of DKA

Expectation: Patient should be eating and drinking and back on normal insulin

- If DKA is not resolved identify and treat the reasons for failure to respond
- Convert to subcutaneous regime when biochemically stable (blood ketones <0.3 mmol/L, pH >7.3) and the patient is ready and able to eat.

Do not discontinue intravenous insulin infusion until 30 minutes after subcutaneous short acting insulin has been given.

Calculating subcutaneous insulin dose in insulin-naïve patients; Calculating a Basal Bolus (QID) Regimen.

- Estimate Total Daily Dose (TDD) of Insulin. The TDD can be calculated by multiplying the patient's weight (in kg) by 0.5 to 0.75 units.
- Use 0.75 units/kg for those thought to be more insulin resistant e.g. obese, acanthosis nigricans
- Example: a 80 kg person would require approximately 80 x 0.5 units or 40 units in 24 hours
- Give 50% of total dose at bedtime in the form of long acting insulin and divide remaining dose equally between pre-breakfast, pre-lunch and pre-evening meal.
  E.g. Short-acting insulin 7u tid & 20 units bedtime

- Modified from Management of DKA in Adults, NHS Trafford Diabetes, January 2012. [248 (Level III)]

4.3 Hyperglycaemic Hyperosmolar State

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

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

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

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

Diagnostic Criteria of HHS [249 (Level III)]

- Hypovolaemia
- Marked hyperglycaemia (BG >30 mmol/L)
- Osmolality >320 mosmol/kg

Other Important Clinical Features [249 (Level III)]

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

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

- The presence of acute cognitive impairment may be associated with cerebral oedema in severe cases or to the presence of significant electrolyte disturbances, hyperosmolality (>330 mosmol/kg), sudden drop in osmolality, severe dehydration, infection and sepsis, hypoglycaemia during treatment, and renal failure.

- Clinical features of dehydration in the patient with HHS can be deceptive and may not be reflective of the seriousness of the fluid depletion. This is because hypertonicity leads to preservation of intravascular volume, causing movement of water from intracellular to extracellular space. [260 (Level III)]

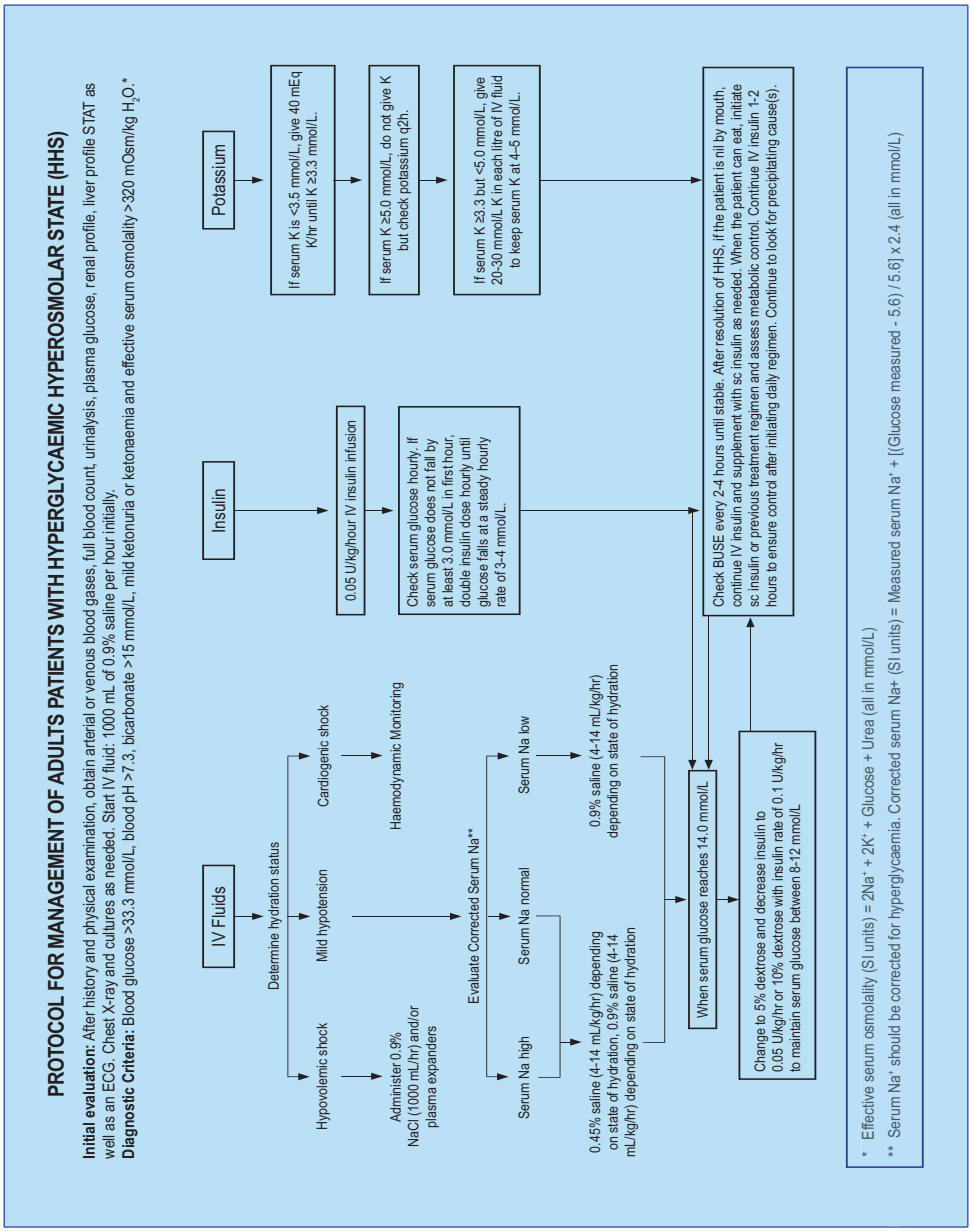
- Precipitating factors for HHS are:
  a) Infections and sepsis
  b) Thrombotic stroke
  c) Intracranial haemorrhage
  d) Silent myocardial infarction
  e) Pulmonary embolism

Management goals

The goals of treatment of HHS are to treat the underlying cause as well as to gradually and safely:

- Normalise the osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose
- Prevention of complications

Algorithm 8: Management of T2DM with Hyperglycaemic Hyperosmolar State



- Modified from Umpierrez GE, Murphy MB, Kitabchi AE. Diabetic Ketoacidosis and Hyperglycaemic Hyperosmolar Syndrome. Diabetes Spectrum, 2002. [261 (Level II-2)]

Principles of treatment

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

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

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

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

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

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

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

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

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

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

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

SECTION 5 MANAGEMENT OF CHRONIC COMPLICATIONS

5.1 Retinopathy

Introduction

- Prevalence of diabetic retinopathy (DR) is closely linked to the duration of diabetes.
- At diagnosis, less than 5% will have retinopathy while the prevalence rises to 40–50% after 10 years. About 60% patients with T2DM have some degree of retinopathy after 20 years of the disease. [262 (Level III)]
- In Malaysia, the prevalence of DR from the 2007 Diabetic Eye Registry was 36.8%. [263 (Level III)] However, other unpublished local data obtained from primary care screening centres showed a prevalence ranging between 12.3% and 16.9%. [264,265 (Level III)]
- Screening and early treatment can prevent substantial visual loss in many cases.
- The initial assessment should be conducted for all patients at the time of diagnosis of T2DM and annually thereafter. [266,267 (Level III)]
- Pregnant women with T2DM should have a retinal examination during each trimester. [268 (Level II-3)] DR screening is not required for GDM. [266,269 (Level II-3)] However, if GDM is diagnosed in the first trimester of pregnancy, screening should be as per pre-existing DM.

Eye Examination

- Visual acuity is assessed with a Snellen chart and any refractive error corrected with a pinhole in addition to asking the patient to wear bifocals or glasses for presbyopia.
- A non-mydriatic fundus camera should be used as a screening tool for DR. [270 (level II-2)] A two field fundus photo (central and peripheral) assessment should be performed. [270 (Level II-2)]
- When there is no access to a fundus camera, an ophthalmoscope should be used for screening DR.
- Tropicamide 1% should be used for pupillary dilatation in selected cases by trained personnel. [270 (Level II)]

Treatment

- The mainstay of current treatment involves risk factor modification by tight control of blood glucose, blood pressure and serum lipids. [271-273 (Level I)]
- Other modalities of risk factor modification include diet, exercise and smoking cessation. [20 (Level I)]
- The presence of retinopathy is not a contraindication to aspirin therapy for cardiovascular disease prevention, as this therapy does not increase the risk of retinal bleeding. [274 (Level I)]
- Laser photocoagulation remains the standard practice for treating DR. Stages of DR which require treatment includes severe non-proliferative DR, proliferative DR, advance diabetes eye disease and diabetic macular edema (DME). [275 (Level II)]

- Referral to an ophthalmologist is necessary for the following situations: [267,270,275,276 (Level III)]
  a) Severe non-proliferative DR
  b) Any level of diabetic maculopathy
  c) Any proliferative DR
  d) Unexplained visual loss
  e) If screening examination cannot be performed including ungradable fundus photo

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

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

Table 34: Criteria for Urgent Referral

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

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

Recommendations: Retinopathy

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

5.2 Nephropathy

Introduction

- Diabetic nephropathy (DN) is a major cause of chronic kidney disease (CKD) contributing to 58% of new patients requiring dialysis in 2012. [279 (Level II-3)] DN is also a major risk factor for cardiovascular morbidity and mortality.

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

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

Screening

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

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

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

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

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

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

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

Management

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

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

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

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

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

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

Table 35: Stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2 BSA)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 or dialysis

GFR = glomerular filtration rate; BSA = body surface area

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

• Adapted from National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease. [292 (Level III)]

Referral to Nephrologist

(Adapted from Malaysian Clinical Practice Guidelines for the Chronic Kidney Disease in Adults [293 (Level III)])

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

a) Estimated GFR <30 mL/min or serum creatinine >200 µmol/L
b) Heavy proteinuria (urine protein ≥3 g/day or urine protein: creatinine ratio (uPCR) ≥0.3 g/mmol)
c) Haematuria
d) Rapidly declining renal function (loss of glomerular filtration rate/GFR >5 mL/min/1.73 m^2 in one year or >10 mL/min/1.73 m^2 within five years)
e) Resistant hypertension (failure to achieve target blood pressure despite three antihypertensive agents including a diuretic)
f) Suspected renal artery stenosis

g) Other suspected causes of CKD (primary glomerular disease, genetic or uncertain causes of CKD)
h) Pregnant or when pregnancy is planned

Recommendations: Management of Nephropathy

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

5.3 Neuropathy

Introduction

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

Diabetic peripheral neuropathy

- Diabetic peripheral neuropathy (DPN) may be defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. [294 (Level III)]
- DPN may be asymptomatic in a large proportion of cases (up to 50%) [295 (Level III)] and requires clinical examination to document/unveil its existence. It causes or contributes to significant morbidity and mortality. [294,295 (Level III)]
- Studies from tertiary centres showed that prevalence of DPN ranged between 50 to 80%. [296,297 (Level II-3)]

Screening and Diagnosis

Neuropathy should be assessed with:

- 10-g monofilament; and one other modality:
  a) pin prick
  b) vibration sense using a 128-Hz tuning fork
  c) ankle reflexes
  d) vibration perception threshold testing using a biothesiometer
- The above increases the sensitivity of detecting peripheral neuropathy by 87%. [298-301 (Level II-3)]
- These bedside tests should be repeated at least annually.

Treatment

- Tight glycaemic control has not shown any benefit in preventing DPN but has modest effect in slowing progression without neuronal loss reversal.
- No pharmacological therapy has been shown to be effective in treating DPN.
- Drugs approved for pain associated with DPN include pregabalin, gabapentin, amitriptyline, duloxetine and venlafaxine as first line therapy; tramadol as a second line therapy. [302 (Level III)] Topical treatment (e.g. capsaicin cream, lidocaine 5% patch) may be added to systemic treatment at any time. [303 (Level III)]

Diabetic Autonomic Neuropathy

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

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

Treatment

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

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

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

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

Recommendations: Neuropathy
1. Assessment for peripheral neuropathy should be performed at diagnosis and repeated annually. *[Grade C]*
2. Drugs approved for neuropathic pain include pregabalin, gabapentin, amitriptyline, duloxetine and venlafaxine as first line therapy; tramadol as a second line therapy. *[Grade C]*
3. Tight control of blood sugar and cardiovascular risks have been shown to reduce the progression and development of autonomic neuropathy. *[Grade B]*

5.4 Coronary Heart Disease

Introduction

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

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

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

- Among those above the age of 60, there is a similar occurrence of MI in T2DM patients and in those without T2DM who had previous MI, thus giving rise to the notion that T2DM is a CHD-defining disease. As such, we should manage cardio-metabolic risks associated with T2DM and CHD in T2DM aggressively. [312,313] (Level II-2)

Screening

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

- In asymptomatic patients, routine screening for coronary artery disease is not recommended because it does not improve outcome as long as cardiovascular disease risk factors are treated. [315] (Level I)

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

- T2DM patients with peripheral or cerebrovascular disease should be screened for CHD. [312,313] (Level I)

Recommendations: Coronary Heart Disease

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

Aspirin for Primary Prevention of Cardiovascular Disease in People with Diabetes

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

- Six well-controlled trials, including the Women's Health Study and Physicians' Health Study, have shown no benefit of aspirin in primary prevention even for at risk patients. [317,318] (Level I)

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

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

Recommendations: Aspirin for Primary Prevention of Cardiovascular Disease in Patients with Diabetes

1. Primary prevention of CVD with low dose aspirin (100 mg) is not recommended in patients with diabetes unless they are above 65 years. *[Grade A]*

5.5 Cerebrovascular Disease

- Patients with diabetes mellitus have approximately twice the risk of ischaemic stroke compared to those without diabetes. In addition, the risk of stroke associated with diabetes is higher in women than in men. [312,313] (Level II-2) Dyslipidaemia, endothelial dysfunction, and platelet and coagulation abnormalities are among the risk factors that may promote the development of carotid atherosclerosis in diabetics.

- For glycaemic control in a patient admitted with acute stroke, please refer to **SECTION 6.1**. For further details, please refer to the Malaysian Clinical Practice Guidelines on the Management of Ischaemic Stroke, 2012. [319] (Level III)

5.6 Diabetic Foot

Introduction

- Foot ulcerations and amputations are major causes of morbidity and mortality in patients with diabetes. The prevalence of diabetic foot ulcer is 15% over the course of the disease [2] (Level II-2), while the prevalence of lower limb amputation was 4.3%. [320] (Level III)

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

Risk Factors for Foot Ulcers [321] (Level III)

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

Prevention of foot ulcers

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

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

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

- The feet should be examined at least once annually or more often in the presence of risk factors. [322] (Level III)

- Relevant education for patients: [323 (Level III)]
  a) In the presence of feet with reduced sensation, look at feet daily using a mirror to detect early ulcerations.
  b) Wear flat, soft and well-fitting shoes to avoid callosities.
  c) Ensure no foreign objects are in the shoes before putting feet in.
  d) Have one pair of shoes for indoor use.

Management

- An ulcer in a patient with any of the above risk factors will warrant an early referral to a specialist for shared care.

- Ulcers with cellulitis will require antibiotics.

- Trauma induced ulcers with no other risk factors will require the standard wound care and close follow-up until full recovery.

- A multidisciplinary approach is recommended for patients with foot ulcer and high-risk feet (e.g. dialysis patients, those with charcot's foot, prior ulcers or amputation).

Recommendations: Diabetic Foot

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

5.7 Sexual Dysfunction

5.7.1 Erectile Dysfunction

Introduction

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

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

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

Screening and Diagnosis

- All adult diabetic males should be asked about ED since many patients do not voluntarily offer the history. [344 (Level II-3)] At the same time, they should also be screened for any symptoms or signs of

hypogonadism such as decreased libido, absence of early morning erection, testicular or muscle atrophy. In those with clinical features of hypogonadism, early morning serum testosterone should be performed. [345,346,347 (Level III)]

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

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

Treatment

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

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

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

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

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

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

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

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

5.7.2 Female Sexual Dysfunction

Introduction

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

- FSD is estimated to occur in 24–75% in diabetic women. [356-364] (Level III)

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

Screening and Diagnosis

- All diabetic women should be asked about sexual dysfunction.

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

- The patient's medical, surgical, social and psychiatric history should also be obtained.

Figure 6: Sexual Symptom Checklist for Women

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: o Little or no interest in sex o Decreased genital sensation (feeling) o Decreased vaginal lubrication (dryness) o Problem reaching orgasm o Pain during sex o Other: _____
4. Would you like to talk about it with your doctor? Yes / No

- Adapted from Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med. 2010. [367] (Level III)

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

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

- Gynaecological examination should be performed if indicated.

- Oestrogen deficiency is usually detected by history and examination.

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

- Routine laboratory testing for testosterone and dehydroepiandrosterone (DHEAs) levels are not recommended. [371] (Level III)

Treatment

- Emphasis should be made to treat psychosocial disorders and relationship disharmony.

- Optimisation of glycaemic control.

- Avoid drugs that may affect sexual function:
  a) Beta-blockers, alpha-blockers, diuretics
  b) Tricyclic antidepressants, SSRIs, lithium, neuroleptics
  c) Anticonvulsants
  d) Oral contraceptive pills

- In postmenopausal women, tibolone has been associated with significant increases in sexual desire and arousal. [372] (Level I) Topical lubricants, vaginal moisturisers and local oestrogen application aid with vaginal dryness and dyspareunia.

- Androgen, DHEAs and PDE5 inhibitor are not recommended. [371,373] (Level III)

Recommendations: Female Sexual Dysfunction
1. FSD is common and should be screened and managed where appropriate. *[Grade C]*

5.8 Mental Health Issues in Diabetes

- Rates of depression are increased by 15% in people with diabetes compared to people without diabetes. [374,375] (Level II-2) In a study involving 2508 patients with diabetes from 12 health clinics in Malaysia, 11.5% were found to have depression. [376] (Level II-2)

- Psychological and social factors are important influences on the ability of patients to cope with chronic disease such as diabetes as they may affect the overall success of management.

- One of the best opportunities to address these are at the time of diagnosis or first presentation. Other times include during scheduled clinic visits and hospitalisations. It is also pertinent to re-assess the psychosocial status at diagnosis of complications, when glucose control is out of control and when there are suggestions that compliance to the diabetes regimen has been compromised.

- The pressures of dealing with a chronic and complex condition like diabetes have been associated with a higher incidence of depression. It resulted in reduced quality of life and increased distress levels as self-care management is affected in patients with higher depressive symptoms.

- Depression has been shown to affect glycaemic control and fluctuations in glucose levels can also aggravate depression. Depression and diabetes are also associated with a significantly increased all-cause and CVD-related mortality.

- Symptoms to look for may include the prolonged period of moodiness with any or all of the following:
  a) Appetite changes
  b) Loss of interest in daily activities
  c) Feeling of despair
  d) Inappropriate sense of guilt
  e) Sleep disturbance
  f) Weight loss

g) Suicidal thoughts

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

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

Recommendations: Mental Health Issues in Diabetes

1. Assessment of psychological and social wellbeing should be performed as part of continuing diabetes management; at diagnosis, onset of complications, when diabetes is out of control and whenever indicated. *[Grade C]*

SECTION 6 DIABETES IN SPECIAL POPULATIONS

6.1 Management of Type 2 Diabetes Mellitus in Acute Illnesses, Stress and Surgery

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

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

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

Diagnosis of Diabetes and Stress Hyperglycaemia in the Acute Illness

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

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

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

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

- During hospital admission, OADs should be stopped for the following:

a) Poor oral intake
b) Acute kidney injury
c) Exposure to intravenous contrast dye (specifically for those on metformin)
d) Illness becomes critical
e) Organ failure e.g. renal failure, liver failure, heart failure

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

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

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

Glycaemic Control in Critically-ill Patients

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

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

Table 36: Glycaemic Targets in Critically-ill Patients

Patient's Setting / Condition	Target Range of Glycaemic Control	Management
Intensive care unit [390] (Level II-3) 388,391 (Level I)	7.8-10.0 mmol/L	• Intravenous insulin infusion with intensive glucose monitoring • Avoid hypoglycaemia • Treat preclinical condition
Acute myocardial infarction (AMI) [392-396] (Level I)	7.0-10.0 mmol/L	• Intravenous insulin infusion with intensive glucose monitoring • Avoid hypoglycaemia • Treatment per AMI
Acute ischaemic stroke [397] (Level I)	7.0-10.0 mmol/L	• Avoid hypoglycaemia • Use insulin if OAD(s) cannot achieve target
Congestive cardiac failure (CCF) [398] (Level II-3) 399 (Level I)	7.0-10.0 mmol/L	• Metformin is contraindicated in moderate-severe CCF • As per treatment for heart failure • Glycaemia tend to improve with resolution of heart failure
Diabetic ketoacidosis	Please refer to **Section 4.2**	
Hyperglycaemic hyperosmolar state	Please refer to **Section 4.3**	

Glycaemic control in major surgery

- Acute hyperglycaemia during major surgery increases postsurgical complications, morbidity and mortality.
- Tight glycaemic control to achieve normoglycaemia while avoiding hypoglycaemia is recommended.

Table 37: Glycaemic Targets in Patients Undergoing Surgery

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

Insulin

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

Special Clinical Situations

Patients receiving enteral or parenteral feedings [387] (Level III)

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

- Alternatively, use a long-acting, less peak basal insulin alone (once-daily glargine or twice daily detemir). For basal-bolus regime, approximately 50% of the TDD is provided as basal insulin and

50% as bolus insulin, which is administered in divided doses. The dose of insulin is adjusted based on BG monitoring results.

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

Patients receiving corticosteroid therapy

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

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

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

Transition from hospital to home

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

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

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

6.2 Diabetes in Pregnancy and Gestational Diabetes Mellitus

Pre-conception Counseling

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

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

- The discussion should include the following points:
  a) Pregnancy has to be planned and to occur only when the woman has good glycaemic control, has had appropriate assessment and management of comorbidities, and has discontinued potentially unsafe medications during pregnancy.
  b) The importance of smoking cessation.
  c) The time, commitment and effort required by the patient in both self-management and engagement with the health care team.
  d) The importance of notifying the health care team without delay in the event of conception.

Pre-pregnancy Management

- Keep the A1c as normal as possible (<6.5%). [415] (Level II-2)

- Weight reduction in those overweight and obese before pregnancy.

- Folic acid supplementation should be started 3 months before withdrawal of contraception. [416] (Level I)

- Women on OAD(s) can be switched to insulin for better glycaemic control before planning pregnancy.

- Insulin treated women should be on multiple daily doses (basal-bolus) of insulin.
  a) Multiple daily doses of short-acting human insulin have been used safely and effectively.
  b) Rapid acting insulin analogues may be used to achieve better 1-hour postprandial glycaemic control with less hypoglycaemia although perinatal outcomes are similar to human insulin. [417] (Level II-1)
  c) Insulin detemir has similar efficacy as NPH insulin but with less nocturnal hypoglycaemia.
  d) Insulin glargine has no RCT data but observational data suggest no adverse effects on pregnancy.

- Screen for diabetic retinopathy and treat appropriately prior to conception. [418] (Level II-2)

- Screen for diabetic nephropathy prior to pregnancy. Women with significantly reduced e-GFR should be counselled by a nephrologist for specific risk of worsening renal function during pregnancy.

- Satisfactory BP control of <130/80 mm Hg before pregnancy is necessary. Common medications used in diabetes such as ACE-inhibitors and ARB should be discontinued upon confirmation of pregnancy. Antihypertensive medications safe to use during pregnancy are methyldopa, labetalol, nifedipine, diltiazem and prazosin.

- Statin should be discontinued during pregnancy as the safety is not known.

- Patient with multiple cardiovascular risk factors should undergo CV risk assessment prior to withdrawal of contraception. Myocardial infarction during pregnancy is associated with adverse maternal and foetal outcomes. [419] (Level III)

Gestational Diabetes Mellitus

- Gestational diabetes mellitus (GDM) is any degree of glucose intolerance which is first recognised during pregnancy, whether or not the condition persisted after pregnancy.

- The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that risk of adverse maternal, foetal, and neonatal outcomes continuously increased as a function of maternal glycaemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. [420] (Level I)

Screening and Diagnosis for GDM

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

recommendation to screen individuals at high risk of developing GDM at booking should be adhered to.

- In general, screening should be done at booking for any pregnant women who have the following risk factors:
  a) BMI >27 kg/m^2
  b) Previous macrosomic baby weighing ≥4 kg
  c) Previous gestational diabetes mellitus
  d) First-degree relative with diabetes
  e) History of unexplained intrauterine death
  f) History of congenital anomalies
  g) Glycosuria at the first or any prenatal visit
  h) Current obstetric problems (essential hypertension, pregnancy-induced hypertension, polyhydramnios and current use of steroids)

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

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

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

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

Table 38: Diagnostic Criteria for GDM

Diagnosis	FPG (mmol/L)	2-h Value (mmol/L)
Gestational diabetes mellitus	≥5.1*	≥7.8**

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

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

Management of diabetes in pregnancy

Nutrition

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

Weight Management

- Energy prescription should be individualised based on pre-pregnancy body weight.

a) For women with normal pre-pregnancy weight, caloric prescription should be as per normal pregnancy (35 kcal/kg body weight).
b) For overweight/obese women, moderate caloric restriction (25 kcal/kg body weight) is advocated without inhibiting foetal growth, birth weight or inducing ketosis. [4] (Level I)
c) Carbohydrate intake should be limited to 45% of total calories.
d) Recommended weight gain is shown in **Table 40**.

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

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

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

Insulin therapy

- Insulin therapy should be considered if the blood glucose targets are not met 1-2 weeks after introducing changes to diet and initiating exercise. [421] (Level III)
- The best insulin regime is multiple daily injections for better glycaemic control during pregnancy.
- In the first trimester there is often a decrease in the total daily dose of insulin. In the second trimester, rapidly increasing insulin resistance requires a biweekly increase in insulin dose to achieve glycaemic targets. [4] (Level III)
- Long-acting insulin analogues may be used in cases of repeated nocturnal hypoglycaemia. [426] (Level I)
- Patients who are admitted for short-term corticosteroid therapy should be monitored closely for any abnormal glucose levels and insulin should be instituted when indicated.

Table 40: Initiating Insulin Therapy in Pregnancy

Glycaemic Abnormality	Suggested Insulin Type and Dose
FPG >5.3 mmol/L	• Start 0.2 units/kg of intermediate-acting insulin at bedtime, increase by 2 units every 3 days until targets are reached.
1-hour postprandial >7.8 mmol/L 2-hour postprandial >6.7 mmol/L	• Start 6 units of short-acting insulin, increase by 2 units every 3 days until targets are reached. • If pre-prandial short-acting insulin dose exceeds 16 units TDS, consider adding 6-10 units intermediate-acting insulin in the morning and titrate accordingly until targets are achieved.

Self-monitoring of blood glucose (SMBG)

- Important in all pregnant women with GDM.

- Monitoring should be done at the following times (spread out over a few days):
  a) Fasting (following an 8-hour of overnight fast) and before each meal.
  b) 1 or 2 hours after the start of each meal (post-prandial).
  c) Bedtime and during the night if indicated.

- More frequent monitoring is essential in those who are poorly controlled.

- Monitoring should preferably be done at home. The traditional blood sugar profile (BSP) performed in the hospital may not reflect the actual day-to-day blood sugar levels.

Table 41: Blood Glucose Targets in Pregnancy

Timing of Blood Glucose	Target Value (mmol/L)
Fasting or pre-prandial	≤5.3
1 hour after the start of a meal	≤7.8
2 hours after the start of a meal	≤6.7

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

OAD therapy

- Published data suggest that the use of metformin in GDM is not associated with any birth defects, pre-ecclampsia or any adverse maternal nor foetal outcomes.

- Based on two recent systematic analysis and meta-analysis, the use of metformin in GDM leads to better maternal outcomes in terms of total weight gain, postprandial blood glucose and pregnancy-induced hypertension; while foetal outcomes were better in terms of severe neonatal hypoglycaemia but worse in terms of preterm birth. Among these variables, weight gain, pregnancy-induced hypertension and neonatal hypoglycaemia were considered highest priority in evaluating the role of metformin in GDM. [427-429 (Level I)]

- The use of metformin during pregnancy in women with polycystic ovarian syndrome is associated with reductions in miscarriage in early pregnancy, weight, fasting serum insulin levels and the incidence of gestational diabetes. [421 (Level III)]

- In view of the above findings, metformin may be offered to well-informed pregnant women after discussion on the safety and the off label use of it.

- The use of glibenclamide in GDM is associated with increased risk of neonatal hypoglycaemia, high maternal weight gain and macrosomia. [428 (Level I)]

Intrapartum

- Monitor capillary plasma glucose every hour to maintain blood glucose levels between 4-7 mmol/L.

- Insulin infusion should be initiated if the capillary blood glucose is not maintained between 4-7 mmol/L. [421 (Level III)]

Post partum

- Insulin requirements drop immediately after delivery by 60-75%. [430] (Level III)
- When breastfeeding, if glycaemic control is inadequate with diet therapy alone, insulin therapy should be continued at a lower dose.
- Most women diagnosed with GDM should be able to discontinue their insulin immediately after delivery.
- In non-breastfeeding mothers, OAD agents can be continued.
- Low dose metformin can be safely used in nursing mothers. [82] (Level II-2)
- Patients should be counselled regarding appropriate contraception.
- Those whose blood sugar normalised immediately after delivery should have a mOGTT performed 6 weeks later. A1c may be falsely elevated in those who are taking iron supplements.
- Women should be informed of the risk of GDM in future pregnancies and advised to have a mOGTT when planning future pregnancies.
- Women with a history of GDM should have annual screening for diabetes. Lifestyle modifications or metformin therapy post-GDM has been shown to prevent the development of diabetes. [431] (Level I)

Recommendations: Diabetes in Pregnancy and Gestational Diabetes Mellitus
1. A1c of <6.5% should be targeted before and during pregnancy for those with a history of diabetes. *[Grade C]*
2. Universal screening should be performed on all pregnant women between week 24 to 28 of gestation using mOGTT. However, in facilities where this is not feasible, recommendation no. 3 below should be adhered to. *[Grade C]*
3. Women with risk factor(s) for diabetes should be screened at booking. If the result is normal, mOGTT should be performed 4-6 weeks later. *[Grade C]*
4. For better glycaemic control during pregnancy, the best insulin regime is multiple daily injections. *[Grade C]*
5. The glycaemic targets are ≤5.3 mmol/L, ≤7.8 mmol/L and ≤6.7 mmol/L for pre-prandial, 1-hr post-meal and 2-hr post-meal, respectively. *[Grade C]*
6. Those whose blood sugar normalised immediately after delivery should have a mOGTT performed 6 weeks later. *[Grade C]*
7. Women with a history of GDM should have annual screening for diabetes. *[Grade C]*

6.3 Diabetes Mellitus in Adolescents

Introduction

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

- T2DM usually occur in the second decade coinciding with physiologic pubertal insulin resistance. It is rare in pre-adolescents.

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

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

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

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

Screening and Diagnosis

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

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

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

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

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

Management

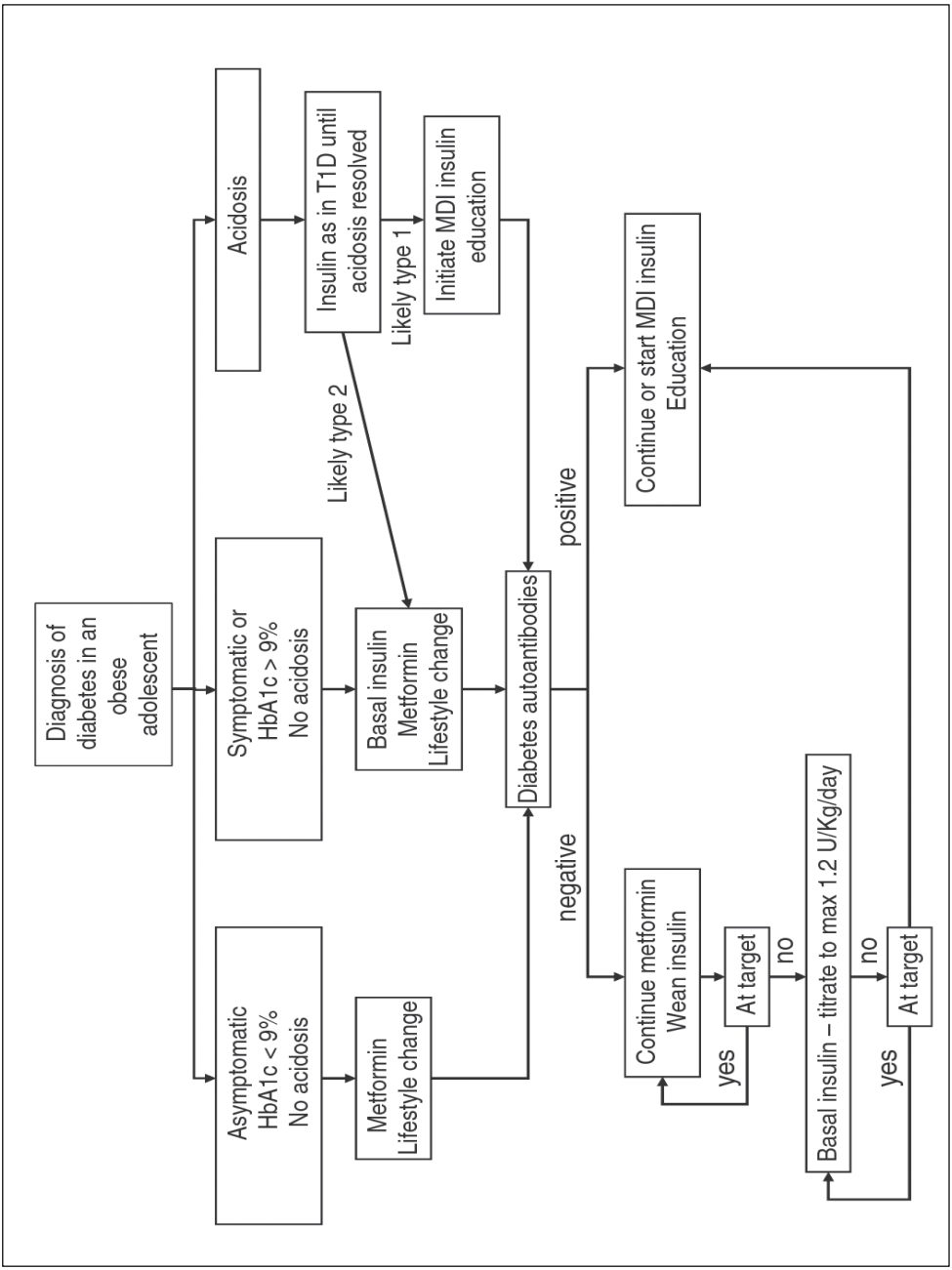
- Management of T2DM in the adolescents should involve the patient and his/her family, emphasising healthy rearing patterns and parental modeling of healthy habits.

- Education and recommendations must be age-appropriate and sensitive to the family's cultural practices and financial resources.

- Lifestyle changes is the cornerstone of T2DM treatment. Such changes need to be permanent.

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

Algorithm 9: Approach to Initial and Subsequent Treatment of Adolescents with T2DM



• Adopted from ISPAD Clinical Practice Consensus Guidelines 2014 Compendium, Pediatric Diabetes 2014:15 (Suppl. 20):26-4

- Goal of treatment is to achieve A1c <6.5%. [442 (Level III)]

- The following monitoring is essential to avoid long term complications: [442 (Level III)]
  a) At diagnosis and annually thereafter:
     i. Test for microalbuminuria or macroalbuminuria
     ii. Examination for retinopathy
     iii. Test for dyslipidaemia
     iv. Evaluation for non-alcoholic fatty liver disease (NAFLD)

  b) At every clinic visit:
     i. Weight and height
     ii. BP (hypertensive if BP ≥95th percentile for age, sex and height percentile) at every visit. Online instructions are available at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf
     iii. Inquiry about puberty, menstrual irregularities and obstructive sleep apnoea
     iv. Psychosocial wellbeing (depression, eating disorder)

Recommendations: Diabetes in Adolescents

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

6.4 Diabetes in the Elderly

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

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

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

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

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

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

Management

- In the elderly with T2DM and established complications, intensive control reduces only the risk of microvascular events but not macrovascular events or mortality. [43,47,443 (Level I)]

- However, better glycaemic control is associated with less disability and better functioning. [444,445 (Level II-2)]

- Postprandial glucose values have been shown to be a better predictor of outcome in elderly patients compared to A1c or preprandial glucose values. [446 (Level I)]

- Greater variability of glucose values is associated with poorer cognition [447] (Level III) despite equivalent glycaemic control. This is not surprising given that hypoglycaemic episodes, are more common in the elderly. [231,448] (Level II-3) Cognitive dysfunction and frailty increases the risk of hypoglycaemia and this causes further impairment of cognitive dysfunction and exacerbate frailty. [289,449,450] (Level III)

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

- The principle of the use of various OADs is similar in the elderly as in younger patients. [451] (Level III) Sulphonylureas should be used with caution because the risk of severe or fatal hypoglycaemia increases exponentially with age and is higher with glibenclamide than gliclazide and glimepiride. [452] (Level III)

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

- Other comorbidities should also be treated to goal.

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

Patient Characteristics / Health Status	Rationale	Reasonable A1c Goal‡	Blood Pressure (mm Hg)	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer life expectancy	≤7.0%	<135/75	LDL-C: • <2.6 mmol/L, or • <1.8 mmol/L (overt CVD) Non-HDL-C: • <3.4 mmol/L HDL-C: • >1.0 mmol/L (male) • >1.2 mmol/L (female) TG: • <1.7 mmol/L
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%	<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%	<150/90	Individualised

- Modified from American Diabetes Association–Standards of Medical Care in Diabetes–2015. [4] (Level III)

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

* Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include debilitating arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction and stroke.
"Multiple" means at least three, but many patients may have five or more.

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

Recommendations: Diabetes in Elderly
1. Postprandial glucose values are a better outcome predictor compared to A1c or preprandial glucose values. *[Grade C]*
2. The glycaemic targets depend on the degree of frailty and overall life expectancy of each individual, rather than chronological age. *[Grade C]*
3. Other comorbidities should be treated to goal. *[Grade C]*

6.5 Diabetes in Ramadan

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

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

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

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

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

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

Preparation Prior to Ramadan

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

- Patients and care-givers should receive education concerning self-care on the following: [455-457] (Level III)

  a) Risks from fasting:
     i. Hypoglycaemia – symptoms and signs, response
     ii. Hyperglycaemia – symptoms and signs, response
     iii. Dehydration
  b) Blood glucose monitoring – during fasting and non-fasting hours
  c) When to stop the fast
  d) Adequate fluid intake
  e) Meal planning and food choices
  f) Physical activity – timing and intensity
  g) Medication administration – timing and dosing
  h) Management of acute complications

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

b) Blood glucose <3.9 mmol/L in the first few hours of fasting (especially if the patient is taking sulfonylureas, meglitinides, or insulin). [457,459 (Level II-2)]
c) Blood glucose >16.7 mmol/L. [458 (Level II-2)]
d) Experience symptoms of hypoglycaemia (patients without SMBG).
e) Symptoms suggestive of severe dehydration such as syncope and confusion.

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

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

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

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

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

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

Physical Activity

- Physical activities and exercise need to be adjusted during Ramadan. The following are recommended: [457,461 (Level III)]
  a) Light and moderate intensity exercise on a regular basis.
  b) Avoid rigorous exercise during daytime because of the risk of hypoglycaemia.
  c) The timing of exercise is preferably performed 1-2 hours after the break of fast.
  d) Performance of *Tarawih* prayers is a form of physical activity.

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

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

Oral Anti-diabetic Agents

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

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

Regimen	*Iftar*	*Sahur*
AGI	No changes	No changes
Biguanides (metformin)	No changes	No changes
DPP-4i	Switch timing to *Iftar*	
Meglitinides	No changes	No changes
SUs	No changes	*Glibenclamide*: Reduce/omit *Gliclazide*: Reduce/omit *Gliclazide MR*: Switch timing to *Iftar* *Glimepiride*: Switch timing to *Iftar*
SGLT2i*	Switch timing to *Iftar*	
TZDs	No changes	

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

Injectable Anti-diabetic Agents

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

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

Regimen	*Iftar*	*Sahur*
GLP-1 RA	Switch timing to *Iftar*	

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

Insulin Therapy During Ramadan

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

Table 45: Insulin Adjustments During Ramadan [157,454,458,463-466 (Level III)]

Insulin Regimen	Adjustment
Basal insulin only	Basal Insulin to be taken at bedtime or after *Iftar* meals. May need dose reduction if there is a risk of daytime hypoglycaemia.
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*. Insulin dose at *Sahur* reduced by 20-50% to prevent daytime hypoglycaemia. or Change to short/rapid acting.
Basal bolus insulin Basal Insulin Bolus/Prandial Insulin	Taken at bedtime or any time after *Iftar* meals. May require a dose reduction if there is daytime hypoglycaemia. *Sahur* – Usual pre-Ramadan breakfast or lunch dose. May require a dose reduction to avoid daytime hypoglycaemia. Lunch – Omit. *Iftar* – Usual pre-Ramadan dinner dose. May require dose increment.
Insulin Pump	*Basal insulin rate*: May require reduction of up to 25%. *Prandial bolus*: According to individualised insulin-to-carbohydrate ratio (ICR).

Recommendations: Diabetes in Ramadan
1. A pre-Ramadan medical assessment of general well-being, glycaemic control, comorbidities and complications should be performed to categorise the patient's risks from fasting as well as to optimise their management. *[Grade C]* 2. Patients and care-givers should receive education concerning self-care on risks of hypoglycaemia, hyperglycaemia and dehydration. *[Grade C]* 3. Anti-diabetic therapies should be individualised during fasting. *[Grade C]*

SECTION 7 PREVENTION OF TYPE 2 DIABETES MELLITUS

7.1 For People At Risk

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

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

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

7.2 Pre-diabetes

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

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

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

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

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

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

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

- Annual assessment / monitoring for glucose tolerance status is recommended. [4 (Level III)]

- Screening and appropriate management of other modifiable cardiovascular risk factors is suggested. [4] (Level III)

Recommendations: Prevention of Type 2 Diabetes Mellitus

1. In patients with IGT, a structured programme of lifestyle modification that includes modest weight loss (5–7% of body weight) and regular moderate-intensity physical activity (at least 150 minutes a week) has been shown to reduce the risk of progression to T2DM. *[Grade A]*
2. Use of pharmacological intervention such as metformin can be considered in those who failed lifestyle intervention (after 6 months). *[Grade C]*

SECTION 8 UNPROVEN THERAPIES IN DIABETES MELLITUS

8.1 Alternative Therapies

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

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

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

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

- The success of some alternative treatments can be difficult to measure. Furthermore, they may result in an additional harm to the patients if the treatment for diabetes is delayed or discontinued. [460 (Level III)]

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

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

- It is very important to inform patients not to replace conventional medical therapy for diabetes with an unproven alternative therapy. Patients need to be cautioned on the potential side effects, drug interactions, and lack of product standardisation, in addition to the increased costs that patients may incur when they use ineffective therapies or delay treatment with proven therapeutic agents.

- One of the issues with the use of alternative therapies is the increasing incidence of kidney and liver failure following the use of such alternative therapies. [479 (Level III)] Medicines for diabetes and other health conditions may need to be adjusted if a person is also using an alternative treatment.

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

8.2 Traditional and Complementary Medicine

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

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

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

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

Recommendations: Unproven Therapies in Diabetes Mellitus

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

SECTION 9 IMPLEMENTING THE GUIDELINES

This section provides some insight into the following:

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

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

9.1 Potential Barriers in Applying the Recommendations

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

i. Patient factors

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

ii. Healthcare professional factors

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

iii. Health services factors

- Inequality in the distribution of manpower, resources and facilities
- Limited resources and facilities
- Budgetary and economic constraints
- Long waiting list for specialist consultation
- Inadequate prioritisation of available manpower and resources

9.2 Necessary Steps To Ensure Effective Compliance to the Guidelines

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

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

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

9.3 Implementation Strategies and Implications to Resources in Applying the Recommendations

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

The materials for the training module would include the following:

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

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

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

Data on the following parameters:

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

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

9.4 Guide to Key Performance Indices (KPI)

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

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

(Proposed Target : 50%)

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

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

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

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

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

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

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

(Proposed Target: 50% for primary care)

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

REFERENCES

1. Institute for Public Health. *The Fourth National Health and Morbidity Survey 2011 (NHMS IV 2011)*. Ministry of Health, Malaysia;2011.
2. Feisul I, Azmi S. *National Diabetes Registry, 2009-2012.* Putrajaya: Non-Communicable Disease Section, Disease Control Division, Department of Public Health, Ministry of Health Malaysia;2013.
3. *DiabCare Malaysia 2013 Action Plan Workshop. Putrajaya, Malaysia. 13th November 2014.*
4. American Diabetes Association. Standards of Medical Care in Diabetes - 2015. *Diabetes Care.* 2015;38(Suppl. 1):S1-S94.
5. De Wit S, Sabin CA, Weber R, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care.* 2008;31(6):1224-1229.
6. Lamberti JS, Crilly JF, Maharaj K, et al. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical antipsychotic drugs. *J Clin Psychiatry.* 2004;65(5):702-706.
7. Hu Y, Liu W, Chen Y, et al. Combined use of fasting plasma glucose and glycated hemoglobin A1c in the screening of diabetes and impaired glucose tolerance. *Acta Diabetologica.* 2010;47(3):231-236.
8. Davidson M, Schriger D, Peters A, et al. Relationship Between Fasting Plasma Glucose and Glycosylated Hemoglobin: Potential for False-Positive Diagnoses of Type 2 Diabetes Using New Diagnostic Criteria. *JAMA* 1999;281:1203-1210.
9. Bonora E, Tuomilehto J. The Pros and Cons of Diagnosing Diabetes with A1c. *Diabetes Care.* 2011;34(Suppl. 2):S184-S190.
10. Kumar PR, Bhansali A, Ravikiran M, et al. Utility of Glycated Hemoglobin in Diagnosing Type 2 Diabetes Mellitus: A Community-Based Study. *J Clin Endocrinol Metab.* 2010;95(6):2832-2835.
11. Carson A, Reynolds K, Fonseca V, et al. Comparison of A1c and Fasting Glucose Criteria to Diagnose Diabetes Among U.S. Adults. *Diabetes Care* 2010;33:95-97.
12. Colagiuri S, Lee C, Wong T, et al. Glycemic Thresholds for Diabetes-Specific Retinopathy: Implications for diagnostic criteria for diabetes. *Diabetes Care.* 2011;34:145-150.
13. Nathan D, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia.* 2007;50:2239-2244.
14. Sabanayagam C, Khoo EY, Lye WK, et al. Diagnosis of Diabetes Mellitus Using HbA1c in Asians: Relationship Between HbA1c and Retinopathy in a Multiethnic Asian Population. *J Clin Endocrinol Metab.* 2015;100(2):689-696.
15. Wan Nazaimoon WM, Md Isa SH, Wan Mohamad WB, et al. Prevalence of diabetes in Malaysia and usefulness of HbA1c as a diagnostic criterion. *Diabet Med.* 2013;30(7):825-828.
16. National Glycohemoglobin Standardization Program (NGSP). Factors that Interfere with HbA1c Test Results. 2014; http://www.ngsp.org/factors.asp. Accessed April 2015.
17. National Glycohemoglobin Standardization Program (NGSP). HbA1c Assay Interferences. 2014; http://www.ngsp.org/interf.asp. Accessed April 2015.
18. National Glycohemoglobin Standardization Program (NGSP). Harmonizing Hemoglobin A1c Testing. 2010; http://www.ngsp.org/bground.asp. Accessed April 2015.
19. Weykamp C, John W, Mosca A, et al. The IFCC Reference Measurement System for HbA1c: a 6-year progress report. *Clinical Chemistry* 2008;54(2):240-248.
20. International Diabetes Federation (IDF). Global Guideline for Type 2 Diabetes 2012; http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf. Accessed April 2015.
21. Selvarajah S, Kaur G, Haniff J, et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. *International Journal of Cardiology* 2014;176:211–218.
22. Australian Diabetes Educators Association (ADEA) & the Dietitians Association of Australia (DAA) Joint Position Statement. The Role of Credentialled Diabetes Educators and Accredited Practising Dietitians in the Delivery of Diabetes Self Management Education and Nutrition Services for People with Diabetes. 2009; http://www.adea.com.au/wp-content/uploads/2009/10/ADEA-DAA-position-statement-re-role-of-CDE-and-dietitians-endorsed-DAA-2009.pdf. Accessed April 2015.
23. Funnell M, Anderson R, Austin A, et al. American Association of Diabetes Educators (AADE) Position Statement: Individualization of Diabetes Self-management Education. *Diabetes Educ.* 2007;33:45-49.
24. Funnell M, Brown T, Childs B, et al. National Standards for Diabetes Self-Management Education. *Diabetes Care.* 2009;32(Suppl. 1):S87-S94.
25. Martin C, Daly A, McWhorter L, et al. American Association of Diabetes Educators (AADE) Position Statement: The Scope of Practice, Standards of Practice and Standards of Professional Performance for Diabetes Educators. *Diabetes Educ.* 2005;31:487-512.
26. Turner R, Holman R, Stratton I, et al. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ.* 1998;317(7160):703-713.
27. The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on The Development and Progression of Long-term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med.* 1993;329:977-986.

28. Norris S, Lau J, Smith S, et al. Self-Management Education for Adults with Type 2 Diabetes: A meta-analysis of the effect on glycemic control. *Diabetes Care.* 2002;25:1159-1171.
29. Ellis S, Speroff T, Dittus R, et al. Diabetes patient education: a meta-analysis and meta-regression. *Patient Educ Couns.* 2004;52:97-105.
30. Gary T, Genkinger J, Guallar E, et al. Meta-analysis of Randomized Educational and Behavioural Interventions in Type 2 Diabetes. *Diabetes Educ.* 2003;29:488-501.
31. Beverly E, Fitzgerald S, Brooks K, et al. Impact of Reinforcement of Diabetes Self-Care on Poorly Controlled Diabetes: A Randomized Controlled Trial. *Diabetes Educ.* 2013;39(4):504-514.
32. Varney J, Weiland T, Inder W, Jelinek G. Effect of hospital-based telephone coaching on glycaemic control and adherence to management guidelines in type 2 diabetes, a randomised controlled trial. *Intern Med J.* 2014;44(9):890-897.
33. Van Dam H, Van der Horst F, Van den Borne B, Ryckman R, Crebolder H. Provider-patient interaction in diabetes care: effects on patient self-care and outcomes. A systematic review. *Patient Educ Couns.* 2003;51(1):17-28.
34. Boule N, Kenny G, Haddad E, et al. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. *Diabetologia.* 2003;46:1071-1081.
35. Boule N, Haddad E, Kenny G, et al. Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus: A Meta-analysis of Controlled Clinical Trials. *JAMA.* 2001;286:1218-1227.
36. Skovlund S, Peyrot M. The Diabetes Attitude, Wishes and Needs (DAWN) Program. A New Approach to Improving Outcomes of Diabetes Care. *Diabetes Spectrum.* 2005;18:136-142.
37. Hill-Briggs F, Gemmell L. Problem solving in diabetes self-management and control: a systematic review of the literature. . *Diabetes Educ* 2007;33:1032-1050.
38. Lustman P, Anderson R, Freedland K, et al. Depression and Poor Glycemic Control: A meta-analytic review of the literature. *Diabetes Care.* 2000;23:934-942.
39. *National Oral Health Survey of Adults 2010 (NOHSA 2010).* Malaysia: Oral Health Division, Ministry of Health Malaysia;2013.
40. Mealey BL, Rose LF. Diabetes mellitus and inflammatory periodontal diseases. *Curr Opin Endocrinol Diabetes Obes.* 2008;15(2):135-141.
41. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. ADVANCE Collaborative Group. *Lancet.* 2007;370(9590):829-840.
42. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. ADVANCE-ON Collaborative Group. *N Engl J Med.* 2014;371(15):1392-1406.
43. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *N Engl J Med.* 2008;358(24):2545-2559.
44. Tuomilehto J, Lindstrom J, Eriksson J, et al. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle Among Subjects with Impaired Glucose Tolerance. *N Engl J Med* 2001;344:1343-1350.
45. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program (DPP) Research Group. *N Engl J Med.* 2002;346(6):393-403.
46. National Institute for Health and Care Excellence (NICE). Type 2 diabetes: The management of type 2 diabetes. 2009; http://www.nice.org.uk/guidance/cg87/resources/the-management-of-type-2-diabetes-975693927877.
47. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. ADVANCE Collaborative Group. *N Engl J Med.* 2008;358(24):2560-2572.
48. The ACCORD Study Group and ACCORD Eye Study Group. Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. *N Engl J Med.* 2010;363:233-244.
49. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2004;114(Suppl. 2):555-576.
50. Inzucchi S, Bergenstal R, Buse J, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. A Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2012;35(6):1364-1379.
51. Franz M, Boucher J, Green-Pastors J, et al. Evidence-Based Nutrition Practice Guidelines for Diabetes and Scope and Standards of Practice. *J Am Diet Assoc.* 2008;108(4):S52-S58.
52. Morrison F, Shubina M, Turchin A. Lifestyle Counseling in Routine Care and Long-Term Glucose, Blood Pressure, and Cholesterol Control in Individuals with Diabetes. *Diabetes Care.* 2012;35(2):334-341.
53. Franz M, Powers M, Leontos C, et al. The Evidence for Medical Nutrition Therapy for Type 1 and Type 2 Diabetes in Adults. *J Am Diet Assoc.* 2010;110(12):1852-1889.
54. Hamman R, Wing R, Edelstein S, et al. Effect of Weight Loss with Lifestyle Intervention on Risk of Diabetes. *Diabetes Care.* 2006;29(9):2102-2107.
55. Curioni C, Lourenco P. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes.* 2005;29:1168-1174.
56. The Look AHEAD Research Group. Reduction in Weight and Cardiovascular Disease Risk Factors in Individuals with Type 2 Diabetes: One-year results of the Look AHEAD trial. *Diabetes Care.*

2007;30(6):1374-1383.
57. Malaysian Dietitians' Association. *Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus.* 2013.
58. Schulze M, Liu S, Rimm E, et al. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr.* 2004;80:348-356.
59. Koning L, Malik V, Rimm E, Willett W, Hu F. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *Am J Clin Nutr* 2011;93(6):1321-1327.
60. Malik V, Popkin B, Bray G, et al. Sugar-sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A meta-analysis. . *Diabetes Care.* 2010;33(11):2477-2483.
61. Wheeler M, Pi-Sunyer F. Carbohydrate Issues: Type and Amount. *J Am Diet Assoc.* 2008;108(4):S34-S39.
62. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* Washington, DC: The National Academies Press; 2005.
63. Sheard N, Clark N, Brand-Miller J, et al. Dietary Carbohydrate (Amount and Type) in the Prevention and Management of Diabetes: A statement by the American Diabetes Association *Diabetes Care.* 2004;27(9):2266-2271.
64. Malik V, Schulze M, Hu F. Intake of sugar-sweetened beverages and weight wain: a systematic review. *Am J Clin Nutr.* 2006;84(2):274-288.
65. Larsen R, Mann N, Maclean E, et al. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia.* 2011;54(4):731-740.
66. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev.* 2007(4):CD002181.
67. Van Horn L, McCoin M, Kris-Etherton P, et al. The Evidence for Dietary Prevention and Treatment of Cardiovascular Disease. *J Am Diet Assoc.* 2008;108(2):287-331.
68. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344(1):3-10.
69. Yeh G, Eisenberg D, Kaptchuk T, et al. Systematic Review of Herbs and Dietary Supplements for Glycemic Control in Diabetes. *Diabetes Care.* 2003;26(4):1277-1294.
70. Hartweg J, Perera R, Montori V, Dinneen S, Neil H, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2008 (Jan 23)(1):CD003205.
71. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care.* 2000;23(9):1407-1415.
72. Feinman R, Pogozelski W, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition.* 2015;31(1):1-13.
73. Thomas D, Elliott E. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database Syst Rev.* 2009(1):CD006296.
74. Liu AG, Most MM, Brashear MM, Johnson WD, Cefalu WT, Greenway FL. Reducing the Glycemic Index or Carbohydrate Content of Mixed Meals Reduces Postprandial Glycemia and Insulinemia Over the Entire Day but Does Not Affect Satiety. *Diabetes Care.* 2012;35(8):1633-1637.
75. Brand-Miller J, Hayne S, Petocz P, Colagiuri S. Low-Glycemic Index Diets in the Management of Diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care.* 2003;26(8):2261-2267.
76. Barakatun-Nisak MY, Ruzita AT, Norimah AK, Nor Azmi K, Fatimah A. Acute Effect of Low and High Glycemic Index Meals on Post-prandial Glycemia and Insulin Responses in Patients withType 2 Diabetes Mellitus. *Malaysian Journal of Medicine and Health Sciences.* 2009;5(1):11-20.
77. Chudyk A, Petrella RJ. Effects of Exercise on Cardiovascular Risk Factors in Type 2 Diabetes: A meta-analysis. *Diabetes Care.* 2011;34(5):1228-1237.
78. Balducci S, Zanuso S, Nicolucci A, et al. Effect of an Intensive Exercise Intervention Strategy on Modifiable Cardiovascular Risk Factors in Subjects with Type 2 Diabetes Mellitus: A Randomized Controlled Trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med.* 2010;170(20):1794-1803.
79. Church T, Blair S, Cocreham S, et al. Effects of Aerobic and Resistance Training on Hemoglobin A1c Levels in Patients with Type 2 Diabetes: A Randomized Controlled Trial. *JAMA.* 2010;304(20):2253-2262.
80. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo Segura M, Roqué i Figuls M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2005 Jul 20;3:CD002966.
81. Salpeter SR, Greyber E, Pasternak GA, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Sys Rev.* 2010(4):CD002967.
82. Glatstein MM, Djokanovic N, Garcia-Bournissen F, Finkelstein Y, Koren G. Use of hypoglycemic drugs during lactation. *Can Fam Physician.* 2009;55(4):371-373.
83. Hirst JA, Farmer AJ, Dyar A, Lung TW, Stevens RJ. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia.* 2013;56(5):973-984.
84. Landman GW, de Bock GH, van Hateren KJ, et al. Safety and efficacy of gliclazide as treatment for type 2 diabetes: a systematic review and meta-analysis of randomized trials. *PLoS One.* 2014;9(2):e82880.
85. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest.* 2004;34(8):535-542.
86. Tayek J. SUR receptor activity vs. incidence of hypoglycaemia and cardiovascular mortality with

sulphonylurea therapy for diabetics. *Diabetes Obes Metab.* 2008;10(11):1128-1129; author reply 1129-1130.
87. Harinder C for WHO Secretariat. *Glibenclamide (Review) - Adults. 19th Expert Committee on the Selection and Use of Essential Medicines.* Geneva: World Health Organization (WHO);2013.
88. Black C, Donnelly P, McIntyre L, Royle P, Shepherd Jonathan J, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2007 Apr 18;2:CD004654.
89. Niemi M, Backman JT, Neuvonen M, Neuvonen PJ. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide. *Diabetologia.* 2003;46(3):347-351.
90. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med.* 1994;121(12):928-935.
91. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, SH E. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2007 Jul 18;3:CD006063.
92. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, SH E. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2006 Oct 18;4:CD006060.
93. Zhu Z-N, Jiang Y-F, Ding T. Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials. *Bone.* 2014;68:115-123.
94. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *Bmj.* 2011;342:d1309.
95. Liu J, Wong L. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in patients with stroke or transient ischemic attack. *Cochrane Database of Systematic Reviews.* 2014 Jan 8;1:CD010693.
96. Kahn SE, Haffner SM, Heise MA, et al., for the ADOPT Study Group. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.
97. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione (TZD) Use and Bone Loss in Older Diabetic Adults. *J Clin Endocrinol Metab.* 2006;91(9):3349-3354.
98. Singh S, Loke YK, Furberg CD. Thiazolidinediones and Heart Failure: A teleo-analysis. *Diabetes Care.* 2007;30(8):2148-2153.
99. Gautier JF, Fetita S, Sobngwi E, Salaun-Martin C. Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. *Diabetes Metab.* 2005;31(3 Pt 1):233-242.
100. Gerich J. Pathogenesis and management of postprandial hyperglycemia: role of incretin-based therapies. *Int J Gen Med.* 2013;6:877-895.
101. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired Regulation of the Incretin Effect in Patients with Type 2 Diabetes. *J Clin Endocrinol Metab.* 2011;96(3):737-745.
102. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia.* 2006;49(11):2564-2571.
103. Nonaka K, Kakikawa T, Sato A, et al. Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2008;79(2):291-298.
104. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. *Diabetes Obes Metab.* 2013;15(10):906-914.
105. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. *Curr Med Res Opin.* 2009;25(10):2401-2411.
106. Barnett AH, Patel S, Harper R, et al. Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. *Diabetes Obes Metab.* 2012;14(12):1145-1154.
107. Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A. Comparison of Vildagliptin and Rosiglitazone Monotherapy in Patients with Type 2 Diabetes: A 24-week, double-blind, randomized trial. *Diabetes Care.* 2007;30(2):217-223.
108. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007;9(2):194-205.
109. Ferrannini E, Fonseca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes Obes Metab.* 2009;11(2):157-166.
110. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q. Efficacy and Safety of the Dipeptidyl Peptidase-4 Inhibitor Alogliptin in Patients with Type 2 Diabetes and Inadequate Glycemic Control: A randomized, double-blind, placebo-controlled study. *Diabetes Care.* 2008;31(12):2315-2317.
111. Cook W, Minervini G, Bryzinski B, Hirshberg B. Saxagliptin efficacy and safety in patients with type 2 diabetes mellitus stratified by cardiovascular disease history and cardiovascular risk factors: analysis of 3 clinical trials. *Postgrad Med.* 2014;126(6):19-32.
112. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with Type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized

study. *Diabet Med.* 2011;28(11):1352-1361.
113. Scirica BM, Bhatt DL, Braunwald E, et al., for the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *N Engl J Med.* 2013;369(14):1317-1326.
114. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine.* 2015;373(3):232-242.
115. White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J.* 2011;162(4):620-626.e621.
116. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open.* 2012;2(5):e001007.
117. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2013;159(4):262-274.
118. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2014;70(10):1149-1158.
119. Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab.* 2014;16(10):984-993.
120. Brunton SA. The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. *Int J Clin Pract.* 2015;69(10):1071-1087.
121. US Food and Drug Administration. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. *Safety Announcement* 2015; http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm.
122. Rosenstock J, Ferrannini E. Euglycaemic Diabetic Ketoacidosis: A Predictable, Detectable And Preventable Safety Concern with SGLT2 inhibitors. *Diabetes Care.* 2015;38:1638-1642.
123. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373:2117-2128.
124. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Sys Rev.* 2011(10):CD006423.
125. Iltz JL, Baker DE, Setter SM, Keith Campbell R. Exenatide: An incretin mimetic for the treatment of type 2 diabetes mellitus. *Clin Ther.* 2006;28(5):652-665.
126. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2008;30(8):1448-1460.
127. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients with Type 2 Diabetes. *Diabetes Care.* 2005;28(5):1092-1100.
128. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Sulfonylurea-Treated Patients With Type 2 Diabetes. *Diabetes Care.* 2004;27(11):2628-2635.
129. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea. *Diabetes Care.* 2005;28(5):1083-1091.
130. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med.* 2005;143(8):559-569.
131. Buse JB, Drucker DJ, Taylor KL, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care.* 2010;33(6):1255-1261.
132. Wysham C, Bergenstal R, Malloy J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. *Diabet Med.* 2011;28(6):705-714.
133. Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab.* 2001;281(1):E155-161.
134. Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88(7):3082-3089.
135. Kolterman OG, Kim DD, Shen L, et al. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am J Health Syst Pharm.* 2005;62(2):173-181.
136. Fineman MS, Shen LZ, Taylor K, Kim DD, Baron AD. Effectiveness of progressive dose-escalation of exenatide (exendin-4) in reducing dose-limiting side effects in subjects with type 2 diabetes. *Diabetes Metab Res Rev.* 2004;20(5):411-417.
137. Alves C, Francisco Batel-Merques, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer. *Diabetes Research and Clinical Practice.* 2012;98(2):271-284.
138. Vilsboll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog,

given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care.* 2007;30(6):1608-1610.
139. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet.* 2009;373(9662):473-481.
140. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care.* 2009;32(1):84-90.
141. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia.* 2009;52(10):2046-2055.
142. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet.* 2014;384(9961):2228-2234.
143. Peterson GE, Pollom RD. Liraglutide in clinical practice: dosing, safety and efficacy. *Int J Clin Pract Suppl.* 2010(167):35-43.
144. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care.* 2013;36(9):2489-2496.
145. Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). *Diabetes Obes Metab.* 2013;15(11):1000-1007.
146. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149.
147. Rodbard HW, Blonde L, Braithwaite SS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract.* 2007;13 Suppl 1:1-68.
148. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med.* 1999;130(5):389-396.
149. Ponssen HH, Elte JW, Lehert P, Schouten JP, Bets D. Combined metformin and insulin therapy for patients with type 2 diabetes mellitus. *Clin Ther.* 2000;22(6):709-718.
150. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1999;131(3):182-188.
151. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care.* 2002;25(2):330-336.
152. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. *Diabetes Care.* 2001;24(7):1226-1232.
153. Coniff RF, Shapiro JA, Seaton TB, Hoogwerf BJ, Hunt JA. A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes. *Diabetes Care.* 1995;18(7):928-932.
154. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2008(2):CD006739.
155. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369(14):1327-1335.
156. Marino AB, Cole SW. Alogliptin: Safety, Efficacy, and Clinical Implications. *J Pharm Pract.* 2015;28(1):99-106.
157. Ministry of Health Malaysia. Practical Guide to Insulin Therapy in Type 2 Diabetes Mellitus. 2010.
158. Poitout V, Robertson R. Glucolipotoxicity: Fuel Excess and β-Cell Dysfunction. *Endocrine Reviews.* 2008;29(3):351-366.
159. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med.* 2007;357(17):1716-1730.
160. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet.* 2008;371(9626):1753-1760.
161. Li Y, Xu W, Liao Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care.* 2004;27(11):2597-2602.
162. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care.* 2000;23(8):1130-1136.
163. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2007 Apr 18;2:CD005613.

164. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2006 Apr 19;2:CD003287.
165. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care.* 2005;28(6):1282-1288.
166. Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet.* 2014;384(9950):1265-1272.
167. Peyrot M, Barnett A, Meneghini L, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabetic Medicine.* 2012;29(5):682-689.
168. Phillip M, Battelino T, Rodriguez H, Danne T, Kaufman F. Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2007;30(6):1653-1662.
169. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2010(1):Cd005103.
170. Bergenstal RM, Klonoff DC, Garg SK, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med.* 2013;369(3):224-232.
171. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405-412.
172. Nathan D, Cleary P, Backlund J, et al. Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *New England Journal of Medicine.* 2005;353(25):2643-2653.
173. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C Assay Into Estimated Average Glucose Values. *Diabetes Care.* 2008;31(8):1473-1478.
174. Borg R, Kuenen JC, Carstensen B, et al. Associations between features of glucose exposure and A1C: the A1C-Derived Average Glucose (ADAG) study. *Diabetes.* 2010;59(7):1585-1590.
175. Parrinello CM, Selvin E. Beyond HbA1c and glucose: the role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. *Curr Diab Rep.* 2014;14(11):548.
176. Asian-Pacific Type 2 Diabetes Policy Group and International Diabetes Federation (IDF) Western Pacific Region. *Type 2 Diabetes Practical Targets and Treatments.* 4 ed. Melbourne, Australia: International Diabetes Institute (IDI); 2005.
177. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311(5):507-520.
178. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* 2000;321(7258):412-419.
179. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med.* 2004;351(19):1941-1951.
180. Gerstein H YS, Mann J, et al. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000;355(9200):253-259.
181. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med.* 2004;351(19):1952-1961.
182. Gaede P, Tarnow L, Vedel P, Parving HH, Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. *Nephrol Dial Transplant.* 2004;19(11):2784-2788.
183. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345(12):861-869.
184. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345(12):851-860.
185. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of Time of Day of Blood Pressure–Lowering Treatment on Cardiovascular Risk in Hypertensive Patients With Type 2 Diabetes. *Diabetes Care.* 2011;34(6):1270-1276.
186. Malaysian Society of Hypertension. *Clinical Practice Guidelines: Management of Hypertension.* Ministry of Health, Malaysia;2013.
187. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med.* 1996;335(4):257-265.
188. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360(2):129-139.
189. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet.* 1998;352(9131):854-865.

190. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003;361(9374):2005-2016.
191. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696.
192. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934.
193. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110(2):227-239.
194. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495-1504.
195. American Diabetes Association (ADA). Management of Dyslipidemia in Children and Adolescents With Diabetes. *Diabetes Care.* 2003;26(7):2194-2197.
196. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.
197. NCEP Expert Panel. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics.* 1992;89(3):495-501.
198. Williams CL, Hayman LL, Daniels SR, et al. Cardiovascular health in childhood: A statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2002;106(1):143-160.
199. Rader DJ, Hovingh GK. HDL and cardiovascular disease. *Lancet.* 2014;384(9943):618-625.
200. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis.* 2011;217(2):492-498.
201. Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. *J Cardiovasc Pharmacol.* 2011;57(2):267-272.
202. Loomba RS, Arora R. Prevention of cardiovascular disease utilizing fibrates--a pooled meta-analysis. *Am J Ther.* 2010;17(6):e182-188.
203. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet.* 2010;375(9729):1875-1884.
204. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet.* 2005;366(9500):1849-1861.
205. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362(17):1563-1574.
206. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: A randomized trial. Arterial Disease Multiple Intervention Trial. *JAMA.* 2000;284(10):1263-1270.
207. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med.* 2002;162(14):1568-1576.
208. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011;365(24):2255-2267.
209. Cannon CP, Giugliano RP, Blazing MA, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J.* 2008;156(5):826-832.
210. Guyton JR, Slee AE, Anderson T, et al. Relationship of Lipoproteins to Cardiovascular Events: The AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). *Journal of the American College of Cardiology.* 2013;62(17):1580-1584.
211. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001;345(22):1583-1592.
212. Malaysian Society for the Study of Obesity. *Clinical Practice Guidelines: Management of Obesity.* Ministry of Health, Malaysia;2004.
213. Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med.* 2010;170(17):1566-1575.
214. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight

regain for adults. *Med Sci Sports Exerc.* 2009;41(2):459-471.
215. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care.* 1998;21(8):1288-1294.
216. Lindgarde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. *J Intern Med.* 2000;248(3):245-254.
217. Rowe R, Cowx M, Poole C, McEwan P, Morgan C, Walker M. The effects of orlistat in patients with diabetes: improvement in glycaemic control and weight loss. *Curr Med Res Opin.* 2005;21(11):1885-1890.
218. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* 2005;142(7):532-546.
219. Lakdawala M, Bhasker A. Report: Asian Consensus Meeting on Metabolic Surgery. Recommendations for the use of Bariatric and Gastrointestinal Metabolic Surgery for Treatment of Obesity and Type II Diabetes Mellitus in the Asian Population: August 9th and 10th, 2008, Trivandrum, India. *Obes Surg.* 2010;20(7):929-936.
220. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004;292(14):1724-1737.
221. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* 2009;122(3):248-256.e245.
222. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg.* 2014;149(3):275-287.
223. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. *Diabetic Medicine.* 2001;18(9):690-705.
224. Kedia N. Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. *Diabetes Metab Syndr Obes.* 2011;4:337-346.
225. Slama G, Traynard PY, Desplanque N, et al. The search for an optimized treatment of hypoglycemia. Carbohydrates in tablets, solutin, or gel for the correction of insulin reactions. *Arch Intern Med.* 1990;150(3):589-593.
226. Brodows RG, Williams C, Amatruda JM. Treatment of insulin reactions in diabetics. *JAMA.* 1984;252(24):3378-3381.
227. Clayton D, Woo V, Yale J-F, Committee CDACPGE. Hypoglycemia. *Canadian journal of diabetes.* 2013;37:S69-S71.
228. Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycaemia and frequency of hypoglycaemia in insulin-treated type 2 diabetes. *Diabetes Res Clin Pract.* 2010;87(1):64-68.
229. Gabriely I, Shamoon H. Hypoglycemia in diabetes: common, often unrecognized. *Cleve Clin J Med.* 2004;71(4):335-342.
230. Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care.* 2003;26(4):1153-1157.
231. Munshi MN, Segal AR, Suhl E, et al. Frequent hypoglycemia among elderly patients with poor glycemic control. *Arch Intern Med.* 2011;171(4):362-364.
232. Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. *Diabetes.* 2003;52(5):1195-1203.
233. Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. *Endocr Pract.* 2003;9(6):530-543.
234. Brunton SA. Nocturnal hypoglycemia: answering the challenge with long-acting insulin analogs. *MedGenMed.* 2007;9(2):38.
235. Brod M, Wolden M, Christensen T, Bushnell DM. A nine country study of the burden of non-severe nocturnal hypoglycaemic events on diabetes management and daily function. *Diabetes Obes Metab.* 2013;15(6):546-557.
236. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia.* 2001;44 Suppl 2:S14-21.
237. Holt P. Taking hypoglycaemia seriously: diabetes, dementia and heart disease. *Br J Community Nurs.* 2011;16(5):246-249.
238. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev.* 2008;24(5):353-363.
239. Opie LH, Yellon DM, Gersh BJ. Controversies in the cardiovascular management of type 2 diabetes. *Heart.* 2011;97(1):6-14.
240. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. *Diabetes Care.* 2011;34 Suppl 2:S132-137.
241. Bolognesi R, Tsialtas D, Bolognesi MG, Giumelli C. Marked sinus bradycardia and QT prolongation in a diabetic patient with severe hypoglycemia. *J Diabetes Complications.* 2011;25(5):349-351.
242. Gill GV, Woodward A, Casson IF, Weston PJ. Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes--the 'dead in bed' syndrome revisited. *Diabetologia.* 2009;52(1):42-45.
243. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, Diabetes, and Cardiovascular Events. *Diabetes Care.* 2010;33(6):1389-1394.

244. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care.* 2001;24(5):942-945.
245. Graves EJ, Gillum BS. Detailed diagnoses and procedures, National Hospital Discharge Survey, 1995. *Vital Health Stat 13.* 1997(130):1-146.
246. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc.* 1992;40(11):1100-1104.
247. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. *Diabetes Metab Syndr Obes.* 2014;7:255-264.
248. Stephens; WP, George; A, Kenz; S, Lee K. *The Management of Diabetic Ketoacidosis in Adults.* NHS Trafford Hospital: NHS; january 2012 2012.
249. Scott A, Brennan G, Carey P, et al. *The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes.* United Kingdom: Joint British Diabetes Societies Inpatient Care Group; August 2012 2012. JBDS 06.
250. Ekpebegh CO, Longo-Mbenza B, Akinrinmade A, Blanco-Blanco E, Badri M, Levitt NS. Hyperglycaemic crisis in the Eastern Cape province of South Africa: high mortality and association of hyperosmolar ketoacidosis with a new diagnosis of diabetes. *S Afr Med J.* 2010;100(12):822-826.
251. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes*. *Pediatr Diabetes.* 2005;6(3):129-135.
252. Ekpebegh C, Longo-Mbenza B. Mortality in hyperglycemic crisis: a high association with infections and cerebrovascular disease. *Minerva Endocrinol.* 2013;38(2):187-193.
253. Chung ST, Perue GG, Johnson A, et al. Predictors of hyperglycaemic crises and their associated mortality in Jamaica. *Diabetes Res Clin Pract.* 2006;73(2):184-190.
254. MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. *Intern Med J.* 2002;32(8):379-385.
255. Wang JY, Wang CY, Huang YS, et al. Increased risk of ischemic stroke after hyperosmolar hyperglycemic state: a population-based follow-up study. *PLoS One.* 2014;9(4):e94155.
256. Cokar O, Aydin B, Ozer F. Non-ketotic hyperglycaemia presenting as epilepsia partialis continua. *Seizure.* 2004;13(4):264-269.
257. Raghavendra S, Ashalatha R, Thomas SV, Kesavadas C. Focal neuronal loss, reversible subcortical focal T2 hypointensity in seizures with a nonketotic hyperglycemic hyperosmolar state. *Neuroradiology.* 2007;49(4):299-305.
258. O'Malley G, Moran C, Draman MS, et al. Central pontine myelinolysis complicating treatment of the hyperglycaemic hyperosmolar state. *Ann Clin Biochem.* 2008;45(Pt 4):440-443.
259. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32(7):1335-1343.
260. Bartoli E, Bergamasco L, Castello L, Sainaghi PP. Methods for the quantitative assessment of electrolyte disturbances in hyperglycaemia. *Nutr Metab Cardiovasc Dis.* 2009;19(1):67-74.
261. Umpierrez GE, Murphy MB, Kitabchi AE. Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome. *Diabetes Spectrum.* 2002;15(1):28-36.
262. Organization wH. Prevention Of Blindness From Diabetes Mellitus. Geneva: WHO; 2005:1-36.
263. Goh PP. Status of diabetic retinopathy among diabetics registered to the Diabetic Eye Registry, National Eye Database, 2007. *Med J Malaysia.* 2008;63 Suppl C:24-28.
264. Maziah I AN, Norasyikin M,. Study on Prevalence of Diabetic Retinopathy at Health Clinic Setting (Klinik Kesihatan Cheneh, Kemaman). Malaysia: Ministry Of Health Of Malaysia; 2009.
265. Kamilah K ZA, Anita I. A Study of Diabetic Retinopathy on Diabetic Patient Attending Fundus Camera at KK Hiliran. Scientific Conference, Jabatan Kesihatan Negeri Terengganu: Ministry of Health Malaysia; 2009.
266. American Academy of Ophthalmology Retina/Vitreous Panel. *Preferred Practice Pattern. Diabetic Retinopathy.* San Fransisco, CA: American Academy of Opthalmology;2014.
267. De Micheli A. Italian standards for diabetes mellitus 2007: executive summary : Diabete Italia, AMD Associazione Medici Diabetologi, SID Societa Italiana di Diabetologia. *Acta Diabetol.* 2008.
268. Fong DS, Aiello LP, Ferris FL, 3rd, Klein R. Diabetic retinopathy. *Diabetes Care.* 2004;27(10):2540-2553.
269. Paul Mitchell SF. Guidelines for the Management of Diabetic Retinopathy. *The National Health and Medical Research Council (NHMRC).* 2008.
270. Malaysian Society of Ophthalmology. *Screening of Diabetic Retinopathy.* Ministry of Health Malaysia;2011.
271. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-853.
272. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int.* 2002;61(3):1086-1097.
273. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA.* 2007;298(8):902-916.
274. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA.* 2008;300(18):2134-2141.
275. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. . *Ophthalmology.* 1991;98(5 Suppl.):766-785.

276. The National Collaborating Centre for Chronic Conditions. Type 2 Diabetes: National clinical guideline for management in primary and secondary care (update). *NICE.* 2014:233.
277. Ministry of Health Malaysia. Diabetic Macular Edema (DME) Guidelines. 2014.
278. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med.* 2015;372(13):1193-1203.
279. Malaysian Society of Nephrology. *21th Report of the Malaysian Dialysis and Transplant Registry 2013.* Malaysian Society of Nephrology;2013.
280. Malaysian Society of Nephrology. *Clinical Practice Guidelines: Diabetic Nephropathy.* Ministry of Health, Malaysia;2004.
281. Scottish Intercollegiate Guidelines Network. *Management of Diabetes: A National Clinical Guideline.* Edinburgh: Scottish Intercollegiate Guidelines Network;2010.
282. Chaiken RL, Khawaja R, Bard M, Eckert-Norton M, Banerji MA, Lebovitz HE. Utility of untimed urinary albumin measurements in assessing albuminuria in black NIDDM subjects. *Diabetes Care.* 1997;20(5):709-713.
283. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145(4):247-254.
284. Wright JT, Jr., Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA.* 2002;288(19):2421-2431.
285. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med.* 1995;123(10):754-762.
286. So WY, Kong AP, Ma RC, et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. *Diabetes Care.* 2006;29(9):2046-2052.
287. Appel LJ, Wright JT, Jr., Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med.* 2010;363(10):918-929.
288. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med.* 2003;163(13):1555-1565.
289. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia.* 2009;52(11):2328-2336.
290. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens.* 2009;27(11):2121-2158.
291. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis.* 1998;31(6):954-961.
292. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis.* 2002;39(2 Suppl. 1):S1-266.
293. Malaysian Society of Nephrology. *Clinical Practice Guidelines: Management of Chronic Kidney Disease in Adults.* Ministry of Health, Malaysia;2011.
294. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med.* 1998;15(6):508-514.
295. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care.* 2005;28(4):956-962.
296. Mimi O, Teng CL, Chia YC. The prevalence of diabetic peripheral neuropathy in an outpatient setting. *Med J Malaysia.* 2003;58(4):533-538.
297. Fatimah AB. *Risk determinants of peripheral neuropathy in patients with type II diabetes mellitus attending follow-up clinics at University Kebangsaan Malaysia Medical Center (UKMMC): a cross sectional study.* Penerbit UKM; 2010.
298. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24(2):250-256.
299. Pop-Busui R, Lu J, Brooks MM, et al. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Cohort. *Diabetes Care.* 2013;36(10):3208-3215.
300. Martin CL, Albers J, Herman WH, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care.* 2006;29(2):340-344.
301. Herman WH, Pop-Busui R, Braffett BH, et al. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in Type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med.* 2012;29(7):937-944.
302. Malaysian Association for the Study of Pain. *Management of Neuropathic Pain.* Malaysian Association for Study of Pain;2012.
303. Lindsay TJ, Rodgers BC, Savath V, Hettinger K. Treating diabetic peripheral neuropathic pain. *Am Fam Physician.* 2010;82(2):151-158.
304. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care.* 2010;33(7):1578-1584.

305. Spallone V, Ziegler D, Freeman R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev.* 2011;27(7):639-653.
306. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348(5):383-393.
307. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care.* 1993;16(2):434-444.
308. Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men. A general population study. *Diabetes Care.* 1998;21(4):539-545.
309. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326(6):381-386.
310. Van Belle E, Bauters C, Hubert E, et al. Restenosis rates in diabetic patients: a comparison of coronary stenting and balloon angioplasty in native coronary vessels. *Circulation.* 1997;96(5):1454-1460.
311. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation.* 1997;96(6):1761-1769.
312. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339(4):229-234.
313. Lee CD, Folsom AR, Pankow JS, Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation.* 2004;109(7):855-860.
314. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol.* 2006;47(1):65-71.
315. Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA.* 2009;301(15):1547-1555.
316. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-1339.
317. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352(13):1293-1304.
318. Steering Committee of the Physicians' Health Study Research Group. Final Report on the Aspirin Component of the Ongoing Physicians' Health Study. *N Engl J Med.* 1989;321(3):129-135.
319. Malaysian Society of Neurosciences. *Clinical Practice Guidelines: Management of Ischaemic Stroke.* Ministry of Health, Malaysia;2012.
320. Letchuman GR, Wan Nazaimoon WM, Wan Mohamad WB, et al. Prevalence of diabetes in the Malaysian National Health Morbidity Survey III 2006. *Med J Malaysia.* 2010;65(3):180-186.
321. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment. A report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Phys Ther.* 2008;88(11):1436-1443.
322. King LB. Impact of a Preventive Program on Amputation Rates in the Diabetic Population. *J Wound Ostomy Continence Nurs.* 2008;35(5):479-482.
323. Viswanathan V, Madhavan S, Rajasekar S, Chamukuttan S, Ambady R. Amputation prevention initiative in South India: positive impact of foot care education. *Diabetes Care.* 2005;28(5):1019-1021.
324. NIH Consensus Development Panel on Impotence. Impotence. *JAMA.* 1993;270(1):83-90.
325. Lue TF. Erectile dysfunction. *N Engl J Med.* 2000;342(24):1802-1813.
326. De Berardis G, Franciosi M, Belfiglio M, et al. Erectile dysfunction and quality of life in type 2 diabetic patients: a serious problem too often overlooked. *Diabetes Care.* 2002;25(2):284-291.
327. Fedele D, Coscelli C, Santeusanio F, et al. Erectile dysfunction in diabetic subjects in Italy. Gruppo Italiano Studio Deficit Erettile nei Diabetici. *Diabetes Care.* 1998;21(11):1973-1977.
328. Bacon CG, Hu FB, Giovannucci E, Glasser DB, Mittleman MA, Rimm EB. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. *Diabetes Care.* 2002;25(8):1458-1463.
329. Siu SC, Lo SK, Wong KW, Ip KM, Wong YS. Prevalence of and risk factors for erectile dysfunction in Hong Kong diabetic patients. *Diabet Med.* 2001;18(9):732-738.
330. Cho NH, Ahn CW, Park JY, et al. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. *Diabet Med.* 2006;23(2):198-203.
331. Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. *Urology.* 2004;64(6):1196-1201.
332. Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Fernando DJ, Levy JC. Erectile dysfunction among men with diabetes is strongly associated with premature ejaculation and reduced libido. *J Sex Med.* 2008;5(9):2125-2134.
333. El-Sakka AI, Tayeb KA. Erectile dysfunction risk factors in noninsulin dependent diabetic Saudi patients. *J Urol.* 2003;169(3):1043-1047.
334. Sasaki H, Yamasaki H, Ogawa K, et al. Prevalence and risk factors for erectile dysfunction in Japanese diabetics. *Diabetes Res Clin Pract.* 2005;70(1):81-89.
335. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994;151(1):54-61.

336. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol.* 2000;163(2):460-463.
337. Penson DF, Latini DM, Lubeck DP, Wallace KL, Henning JM, Lue TF. Do impotent men with diabetes have more severe erectile dysfunction and worse quality of life than the general population of impotent patients? Results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction (ExCEED) database. *Diabetes Care.* 2003;26(4):1093-1099.
338. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med.* 1998;338(20):1397-1404.
339. Walsh TJ, Hotaling JM, Smith A, Saigal C, Wessells H. Men with diabetes may require more aggressive treatment for erectile dysfunction. *Int J Impot Res.* 2014;26(3):112-115.
340. Zheng H, Fan W, Li G, Tam T. Predictors for erectile dysfunction among diabetics. *Diabetes Res Clin Pract.* 2006;71(3):313-319.
341. Roth A, Kalter-Leibovici O, Kerbis Y, et al. Prevalence and risk factors for erectile dysfunction in men with diabetes, hypertension, or both diseases: a community survey among 1,412 Israeli men. *Clin Cardiol.* 2003;26(1):25-30.
342. Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. *J Urol.* 2000;163(3):788-791.
343. Matfin G, Jawa A, Fonseca VA. Erectile dysfunction: interrelationship with the metabolic syndrome. *Curr Diab Rep.* 2005;5(1):64-69.
344. Leiblum SR. *Principles and Practice of Sex Therapy.* Vol 1. New York US: The Guilford Press; 2007.
345. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc.* 2012;87(8):766-778.
346. Hackett G, Kell P, Ralph D, et al. British Society for Sexual Medicine guidelines on the management of erectile dysfunction. *J Sex Med.* 2008;5(8):1841-1865.
347. Qaseem A, Snow V, Denberg TD, et al. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2009;151(9):639-649.
348. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997;49(6):822-830.
349. Lim TO, Das A, Rampal S, et al. Cross-cultural adaptation and validation of the English version of the International Index of Erectile Function (IIEF) for use in Malaysia. *Int J Impot Res.* 2003;15(5):329-336.
350. Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. *Int J Clin Pract.* 2006;60(8):967-975.
351. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. *JAMA.* 1999;281(5):421-426.
352. Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. *Diabetes Care.* 2003;26(3):777-783.
353. Saenz de Tejada I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care.* 2002;25(12):2159-2164.
354. Basson R, Berman J, Burnett A, et al. Report of the International Consensus Development Conference on Female Sexual Dysfunction: Definitions and Classifications. *J Urol.* 2000;163(3):888-893.
355. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder.* 5 ed. US2014.
356. Veronelli A, Mauri C, Zecchini B, et al. Sexual dysfunction is frequent in premenopausal women with diabetes, obesity, and hypothyroidism, and correlates with markers of increased cardiovascular risk. A preliminary report. *J Sex Med.* 2009;6(6):1561-1568.
357. Erol B, Tefekli A, Ozbey I, et al. Sexual Dysfunction in Type II Diabetic Females: A Comparative Study. *J Sex Marital Ther.* 2002;28(Suppl. 1):55-62.
358. Doruk H, Akbay E, Cayan S, Akbay E, Bozlu M, Acar D. Effect of diabetes mellitus on female sexual function and risk factors. *Arch Androl.* 2005;51(1):1-6.
359. Abu Ali RM, Al Hajeri RM, Khader YS, Shegem NS, Ajlouni KM. Sexual dysfunction in Jordanian diabetic women. *Diabetes Care.* 2008;31(8):1580-1581.
360. Olarinoye J, Olarinoye A. Determinants of sexual function among women with type 2 diabetes in a Nigerian population. *J Sex Med.* 2008;5(4):878-886.
361. Fatemi SS, Taghavi SM. Evaluation of sexual function in women with type 2 diabetes mellitus. *Diab Vasc Dis Res.* 2009;6(1):38-39.
362. Nowosielski K, Drosdzol A, Sipinski A, Kowalczyk R, Skrzypulec V. Diabetes Mellitus and Sexuality - Does it Really Matter? *J Sex Med.* 2010;7(2 Pt 1):723-735.
363. Dina Muhayidin A, Wong M, Sukor N, Sidi H, Ismail A, Azmi Kamaruddin N. Prevalence of Sexual Dysfunction Among Premenopausal Women With and Without Type 2 Diabetes Mellitus. *Journal of Endocrinology and Metabolism.* 2013;3(1):29-39.
364. Pontiroli AE, Cortelazzi D, Morabito A. Female sexual dysfunction and diabetes: a systematic review and meta-analysis. *J Sex Med.* 2013;10(4):1044-1051.
365. Enzlin P, Rosen R, Wiegel M, et al. Sexual dysfunction in women with type 1 diabetes: long-term findings

from the DCCT/ EDIC study cohort. *Diabetes Care.* 2009;32(5):780-785.
366. Esposito K, Maiorino MI, Bellastella G, Giugliano F, Romano M, Giugliano D. Determinants of female sexual dysfunction in type 2 diabetes. *Int J Impot Res.* 2010;22(3):179-184.
367. Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med.* 2010;7(1 Pt 2):337-348.
368. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther.* 2000;26(2):191-208.
369. Sidi H, Abdullah N, Puteh SE, Midin M. The Female Sexual Function Index (FSFI): validation of the Malay version. *J Sex Med.* 2007;4(6):1642-1654.
370. Hatzichristou D, Rosen RC, Broderick G, et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. *J Sex Med.* 2004;1(1):49-57.
371. Wierman ME, Arlt W, Basson R, et al. Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2014;99(10):3489-3510.
372. Nijland EA, Weijmar Schultz WC, Nathorst-Boos J, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. *J Sex Med.* 2008;5(3):646-656.
373. Basson R, Wierman ME, van Lankveld J, Brotto L. Summary of the Recommendations on Sexual Dysfunctions in Women. *J Sex Med.* 2010;7(1 Pt 2):314-326.
374. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care.* 2008;31(12):2383-2390.
375. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med.* 2006;23(11):1165-1173.
376. Kaur G, Tee GH, Ariaratnam S, Krishnapillai AS, China K. Depression, anxiety and stress symptoms among diabetics in Malaysia: a cross sectional study in an urban primary care setting. *BMC Fam Pract.* 2013;14:69.
377. Rubin R, Biermann J, Toohey B. *Psyching Out Diabetes: A Positive Approach to Your Negative Emotions.* Los Angeles Lowell House; 1999.
378. Polonsky W. *Diabetes Burnout: What to Do When You Can't Take It Anymore*. Alexandria, Virginia: American Diabetes Association; 1999.
379. Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med.* 2006;355(18):1903-1911.
380. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab.* 2002;87(3):978-982.
381. Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax.* 2006;61(4):284-289.
382. Yan CL, Huang YB, Chen CY, Huang GS, Yeh MK, Liaw WJ. Hyperglycemia is associated with poor outcomes in surgical critically ill patients receiving parenteral nutrition. *Acta Anaesthesiol Taiwan.* 2013;51(2):67-72.
383. McAlister FA, Majumdar SR, Blitz S, Rowe BH, Romney J, Marrie TJ. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes Care.* 2005;28(4):810-815.
384. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med.* 2009;37(12):3001-3009.
385. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. *Endocr Pract.* 2009;15(4):353-369.
386. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet.* 2002;359(9324):2140-2144.
387. Houlden R, Capes S, Clement M, Miller D. In-hospital Management of Diabetes. *Canadian Journal of Diabetes.* 2013;37:S77-S81.
388. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* 2009;180(8):821-827.
389. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;125(5):1007-1021.
390. Van den Berghe G, Wouters P, Weekers F, et al. Intensive Insulin Therapy in Critically Ill Patients. *New England Journal of Medicine.* 2001;345(19):1359-1367.
391. Finfer S, Chittock D, Su Y, et al. Intensive versus Conventional Glucose Control in Critically Ill Patients. *New England Journal of Medicine.* 2009;360(13):1283-1297.
392. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J.* 2005;26(7):650-661.
393. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* 1995;26(1):57-65.

394. Malmberg K, Ryden L, Hamsten A, Herlitz J, Waldenstrom A, Wedel H. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. *Eur Heart J.* 1996;17(9):1337-1344.
395. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ.* 1997;314(7093):1512-1515.
396. Malmberg KA, Efendic S, Ryden LE. Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. A report from the multicenter trial: DIGAMI. *Diabetes Care.* 1994;17(9):1007-1014.
397. Bellolio MF, Gilmore RM, Ganti L. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev.* 2014;1:CD005346.
398. Belardinelli R, Cianci G, Gigli M, Mazzanti M, Lacalaprice F. Effects of trimetazidine on myocardial perfusion and left ventricular systolic function in type 2 diabetic patients with ischemic cardiomyopathy. *J Cardiovasc Pharmacol.* 2008;51(6):611-615.
399. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J.* 2003;146(5):848-853.
400. Raucoules-Aime M, Lugrin D, Boussofara M, Gastaud P, Dolisi C, Grimaud D. Intraoperative glycaemic control in non-insulin-dependent and insulin-dependent diabetes. *Br J Anaesth.* 1994;73(4):443-449.
401. Hemmerling TM, Schmid MC, Schmidt J, Kern S, Jacobi KE. Comparison of a continuous glucose-insulin-potassium infusion versus intermittent bolus application of insulin on perioperative glucose control and hormone status in insulin-treated type 2 diabetics. *J Clin Anesth.* 2001;13(4):293-300.
402. Christiansen CL, Schurizek BA, Malling B, Knudsen L, Alberti KG, Hermansen K. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery. Continuous intravenous infusion compared with subcutaneous administration. *Anaesthesia.* 1988;43(7):533-537.
403. Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. *Transplantation.* 2001;72(7):1321-1324.
404. Estrada CA, Young JA, Nifong LW, Chitwood WR, Jr. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg.* 2003;75(5):1392-1399.
405. Bucerius J, Gummert JF, Walther T, et al. Impact of diabetes mellitus on cardiac surgery outcome. *Thorac Cardiovasc Surg.* 2003;51(1):11-16.
406. Ouattara A, Lecomte P, Le Manach Y, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology.* 2005;103(4):687-694.
407. Lipshutz AK, Gropper MA. Perioperative glycemic control: an evidence-based review. *Anesthesiology.* 2009;110(2):408-421.
408. Subramaniam B, Panzica PJ, Novack V, et al. Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. *Anesthesiology.* 2009;110(5):970-977.
409. DiNardo M, Donihi AC, Forte P, Gieraltowski L, Korytkowski M. Standardized glycemic management and perioperative glycemic outcomes in patients with diabetes mellitus who undergo same-day surgery. *Endocr Pract.* 2011;17(3):404-411.
410. Szekely A, Levin J, Miao Y, et al. Impact of hyperglycemia on perioperative mortality after coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg.* 2011;142(2):430-437.e431.
411. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care.* 2011;34(2):256-261.
412. Umpierrez GE, Smiley D, Zisman A, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care.* 2007;30(9):2181-2186.
413. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract.* 2006;12(4):358-362.
414. Anwar A, Salih A, Masson E, Allen B, Wilkinson L, Lindow SW. The effect of pre-pregnancy counselling for women with pre-gestational diabetes on maternal health status. *Eur J Obstet Gynecol Reprod Biol.* 2011;155(2):137-139.
415. Langer O, Conway DL. Level of glycemia and perinatal outcome in pregestational diabetes. *J Matern Fetal Med.* 2000;9(1):35-41.
416. Wilson RD, Johnson JA, Wyatt P, et al. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can.* 2007;29(12):1003-1026.
417. Canadian Diabetes Association (CDA). Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Canadian Journal of Diabetes.* 2013;37(Suppl. 1):S1-S212.
418. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care.* 1995;18(5):631-637.
419. Roth A EU. Acute Myocardial Infarction Associated With Pregnancy. *Journal of the American College of Cardiology.* 2008;52(3):171-180.

420. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991-2002.
421. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. 2015.
422. Hod M, Kapur A, Sacks DA, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *Int J Gynaecol Obstet.* 2015;131 Suppl 3:S173.
423. Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676-682.
424. WHO Guidelines Approved by the Guidelines Review Committee. *Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Geneva: World Health Organization; 2013.
425. Rasmussen KM, Yaktine AL. *Weight Gain During Pregnancy: Reexamining the Guidelines.* Washington (DC): National Academy of Sciences; 2009.
426. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care.* 2010;33(1):29-33.
427. Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of oral antidiabetic drugs in management of gestational diabetes: network meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab.* 2015:jc20144403.
428. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ.* 2015;350:h102.
429. Bennett WL, Robinson KA, Saldanha IJ, Wilson LM, Nicholson WK. High priority research needs for gestational diabetes mellitus. *J Womens Health (Larchmt).* 2012;21(9):925-932.
430. John LK. Insulin therapy in pregnancy. *Textbook of Diabetes and Pregnancy*. 2 ed: CRC Press; 2008:205-216.
431. The Diabetes Prevention Program Research Group. The 10-Year Cost-Effectiveness of Lifestyle Intervention or Metformin for Diabetes Prevention: An intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care.* 2012;35(4):723-730.
432. Dabelea D, Bell RA, D'Agostino RB, Jr., et al. Incidence of diabetes in youth in the United States. *JAMA.* 2007;297(24):2716-2724.
433. Chan JC, Cheung CK, Swaminathan R, Nicholls MG, Cockram CS. Obesity, albuminuria and hypertension among Hong Kong Chinese with non-insulin-dependent diabetes mellitus (NIDDM). *Postgrad Med J.* 1993;69(809):204-210.
434. Wei JN, Sung FC, Li CY, et al. Low Birth Weight and High Birth Weight Infants Are Both at an Increased Risk to Have Type 2 Diabetes Among Schoolchildren in Taiwan. *Diabetes Care.* 2003;26(2):343-348.
435. Hanas R, Donaghue KC, Klingensmith G, Swift PG. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. *Pediatr Diabetes.* 2009;9:512-526.
436. Kitagawa T, Owada M, Urakami T, Tajima N. Epidemiology of type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in Japanese children. *Diabetes Res Clin Pract.* 1994;24(Suppl.):S7-13.
437. Rosenbloom AL. Obesity, Insulin Resistance, beta-Cell Autoimmunity, and the Changing Clinical Epidemiology of Childhood Diabetes. *Diabetes Care.* 2003;26(10):2954-2956.
438. Umpaichitra V, Banerji MA, Castells S. Autoantibodies in children with type 2 diabetes mellitus. *J Pediatr Endocrinol Metab.* 2002;15(Suppl. 1):525-530.
439. Reinehr T, Schober E, Wiegand S, Thon A, Holl R. Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? *Arch Dis Child.* 2006;91(6):473-477.
440. American Diabetes Association. Type 2 Diabetes in Children and Adolescents. *Pediatrics.* 2000;105(3):671-680.
441. American Diabetes Association (ADA). Consensus Statement on Type 2 Diabetes in Children and Adolescents. *Diabetes Care.* 2000;23:381-389.
442. Acerini C, Craig ME, de Beaufort C, Maahs DM, Hanas R. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. *Pediatr Diabetes.* 2014;15(Suppl. 20):26-46.
443. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia.* 2009;52(11):2288-2298.
444. Wang CP, Hazuda HP. Better glycemic control is associated with maintenance of lower-extremity function over time in Mexican American and European American older adults with diabetes. *Diabetes Care.* 2011;34(2):268-273.
445. Kalyani RR, Saudek CD, Brancati FL, Selvin E. Association of diabetes, comorbidities, and A1C with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. *Diabetes Care.* 2010;33(5):1055-1060.
446. Raz I, Ceriello A, Wilson PW, et al. Post hoc subgroup analysis of the HEART2D trial demonstrates lower cardiovascular risk in older patients targeting postprandial versus fasting/premeal glycemia. *Diabetes Care.* 2011;34(7):1511-1513.
447. Rizzo MR, Marfella R, Barbieri M, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. *Diabetes Care.* 2010;33(10):2169-2174.
448. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment

approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ.* 2010;340:b5444.
449. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr., Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA.* 2009;301(15):1565-1572.
450. Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. *Diabetologia.* 2009;52(9):1808-1815.
451. Meneilly GS, Elliott T. Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. *Diabetes Care.* 1999;22(1):112-118.
452. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med.* 1997;157(15):1681-1686.
453. Salti I, Benard E, Detournay B, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care.* 2004;27(10):2306-2311.
454. Al-Arouj M, Assaad-Khalil S, Buse J, et al. Recommendations for management of diabetes during Ramadan: update 2010. *Diabetes Care.* 2010;33(8):1895-1902.
455. Benaji B, Mounib N, Roky R, et al. Diabetes and Ramadan: review of the literature. *Diabetes Res Clin Pract.* 2006;73(2):117-125.
456. Bashir MI, Pathan MF, Raza SA, et al. Role of oral hypoglycemic agents in the management of type 2 diabetes mellitus during Ramadan. *Indian J Endocrinol Metab.* 2012;16(4):503-507.
457. Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with Type 2 diabetes who fast during Ramadan. *Diabet Med.* 2010;27(3):327-331.
458. Pathan MF, Sahay RK, Zargar AH, et al. South Asian Consensus Guideline: Use of insulin in diabetes during Ramadan. *Indian J Endocrinol Metab.* 2012;16(4):499-502.
459. Ibrahim MA. Managing diabetes during Ramadan. *Diabetes Voice.* 2007;52(2):19-22.
460. Noormah MD, Roza S, Zalina A. *Nutritional Therapy as a Complement for Diabetes & Hypertension.* Malaysian Health Technology Assessment Section (MaHTAS): Ministry of Health Malaysia;2013.
461. Karamat MA, Syed A, Hanif W. Review of diabetes management and guidelines during Ramadan. *J R Soc Med.* 2010;103(4):139-147.
462. Almaatouq MA. Pharmacological approaches to the management of type 2 diabetes in fasting adults during Ramadan. *Diabetes Metab Syndr Obes.* 2012;5:109-119.
463. Hui E, Devendra D. Diabetes and fasting during Ramadan. *Diabetes Metab Res Rev.* 2010;26(8):606-610.
464. Bin-Abbas BS. Insulin pump therapy during Ramadan fasting in type 1 diabetic adolescents. *Ann Saudi Med.* 2008;28(4):305-306.
465. Hawli YM, Zantout MS, Azar ST. Adjusting the basal insulin regimen of patients with type 1 diabetes mellitus receiving insulin pump therapy during the Ramadan fast: A case series in adolescents and adults. *Curr Ther Res Clin Exp.* 2009;70(1):29-34.
466. Benbarka MM, Khalil AB, Beshyah SA, Marjei S, Awad SA. Insulin pump therapy in Moslem patients with type 1 diabetes during Ramadan fasting: an observational report. *Diabetes Technol Ther.* 2010;12(4):287-290.
467. Lindstrom J, Louheranta A, Mannelin M, et al. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care.* 2003;26(12):3230-3236.
468. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.* 1997;20(4):537-544.
469. Eriksson KF, Lindgärde F. Prevention of Type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise The 6-year Malmö feasibility study. *Diabetologia.* 1991;34(12):891-898.
470. American Diabetes Association. Standards of Medical Care in Diabetes—2009. *Diabetes Care.* 2009;21(Suppl. 1):S13-S61.
471. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia.* 2006;49(2):289-297.
472. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care.* 1998;21(10):1720-1725.
473. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* 2004;27(1):155-161.
474. Chatterton H, Younger T, Fischer A, Khunti K. Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance. *BMJ.* 2012;345:e4624.
475. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* 2009;374(9702):1677-1686.
476. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet.* 2008;371(9626):1783-1789.
477. Lindstrom J, Peltonen M, Eriksson JG, et al. Improved lifestyle and decreased diabetes risk over 13 years:

long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia.* 2013;56(2):284-293.
478. Angell M, Kassirer JP. Alternative Medicine - The Risks of Untested and Unregulated Remedies. *N Engl J Med.* 1998;339(12):839-841.
479. Ernst E. Complementary medicine: its hidden risks. *Diabetes Care.* 2001;24(8):1486-1488.
480. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA.* 1998;280(18):1569-1575.
481. Egede LE, Ye X, Zheng D, Silverstein MD. The prevalence and pattern of complementary and alternative medicine use in individuals with diabetes. *Diabetes Care.* 2002;25(2):324-329.
482. Ingram M. News: Complementary medicine is booming worldwide. *BMJ.* 1996;313(7050):131-133.
483. American Diabetes Association. American Diabetes Association Position Statement. Unproven Therapy. *Diabetes Care.* 2004;27(Suppl. 1):S135.
484. National Pharmaceutical Control Bureau. Malaysian Guidelines for the Reporting & Monitoring. 2002; http://portal.bpfk.gov.my/index.cfm?menuid=27&parentid=16, April 2015.
485. Huri HZ, Lian GTP, Hussain S, Pendek R, Widodo RT. A survey amongst complementary alternative medicine (CAM) users with type 2 diabetes. *Int J Diabetes & Metabolism.* 2009;17:9-15.
486. Ching SM, Zakaria ZA, Paimin F, Jalalian M. Complementary alternative medicine use among patients with type 2 diabetes mellitus in the primary care setting: a cross-sectional study in Malaysia. *BMC complementary and alternative medicine.* 2013;13(1):148.
487. Dans AM, Villarruz MV, Jimeno CA, et al. The effect of Momordica charantia capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. *J Clin Epidemiol.* 2007;60(6):554-559.
488. Krawinkel MB, Keding GB. Bitter gourd (Momordica Charantia): A dietary approach to hyperglycemia. *Nutr Rev.* 2006;64(7 Pt 1):331-337.
489. Fernandes NP, Lagishetty CV, Panda VS, Naik SR. An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized Momordica charantia fruit extract. *BMC Complement Altern Med.* 2007;7:29.
490. Nakamura Y, Tsumura Y, Tonogai Y, Shibata T. Fecal steroid excretion is increased in rats by oral administration of gymnemic acids contained in Gymnema sylvestre leaves. *J Nutr.* 1999;129(6):1214-1222.
491. Tiwari AK, Rao JM. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospects. *Current Science.* 2002;83(1):30-38.
492. Vuksan V, Sung MK, Sievenpiper JL, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. *Nutr Metab Cardiovasc Dis.* 2008;18(1):46-56.
493. Vuksan V, Sievenpiper JL, Koo VY, et al. American ginseng (Panax quinquefolius L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch Intern Med.* 2000;160(7):1009-1013.
494. Mohamed EAH, Mohamed AJ, Asmawi MZ, Sadikun A, Ebrika OS, Yam MF. Antihyperglycemic effect of Orthosiphon stamineus Benth leaves extract and its bioassay-guided fractions. *Molecules.* 2011;16(5):3787-3801.
495. Ballali S, Lanciai F. Functional food and diabetes: a natural way in diabetes prevention? *Int J Food Sci Nutr.* 2012;63(Suppl. 1):51-61.
496. Sievenpiper JL, Arnason JT, Vidgen E, Leiter LA, Vuksan V. A Systematic Quantitative Analysis of the Literature of the High Variability in Ginseng (Panax spp.): Should ginseng be trusted in diabetes? *Diabetes Care.* 2004;27(3):839-840.
497. Tee ES, Mohd Ismail N, Mohd Nasir A, et al. *Nutrient Composition of Malaysian Foods.* 4th ed. Kuala Lumpur: Institute for Medical Research; 1997.
498. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care.* 2008;31(12):2281-2283.
499. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr.* 2002;76(1):5-56.
500. Mohd Yusof BN, Abd. Talib R, Karim NA, Kamarudin NA, Arshad F. Glycaemic index of four commercially available breads in Malaysia. *International journal of food sciences and nutrition.* 2008;60(6):487-496.
501. Shanita SN, Hasnah H, Khoo C. Amylose and amylopectin in selected Malaysian foods and its relationship to glycemic index. *Sains Malaysiana.* 2011;40(8):865-870.
502. Robert SD, Ismail AA, Winn T, Wolever TM. Glycemic index of common Malaysian fruits. *Asia Pac J Clin Nutr.* 2008;17(1):35-39.
503. American College of Sports Medicine. American College of Sports Medicine Position Stand. Progression Models in Resistance Training for Healthy Adults. *Med Sci Sports Exerc.* 2009;41(3):687-708.

APPENDIX 1: 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
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 (30 g)	281	41	3
Bread (white/wholemeal)	1 slice (30 g)	70	15	1
Biscuits, unsweetened	2 pieces (18 g)	80	14	1
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 tablespoon (28 g)	100	16	1
Condensed milk, sweetened	2 tablespoon (40 g)	126	21	1.5
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	5 small seeds (189 g)	64	12	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

Source: Tee ES, Mohd Ismail N, Mohd Nasir A, et al. Nutrient Composition of Malaysian Foods. Institute for Medical Research (IMR). Kuala Lumpur, 1997. [497 (Level III)]

APPENDIX 2: Food Groups and Exchange List

Cereals, Grain Products and Starchy Vegetables (Each item contains 15 g carbohydrate, 2 g protein, 0.5 g fat and 75 calories)	
Cereals, Grain & Bread	
Rice, white unpolished (cooked)	½ cup or 1/3 Chinese rice bowl
Can be exchanged for	
Rice porridge	1 cup
Kway teow	½ cup or 1/3 Chinese rice bowl
Mee hoon	
Tang hoon	
Spaghetti	
Macaroni	
Mee, wet	1/3 cup
Idli	1 piece (60 g)
Putu mayam	1 piece (40 g)
Thosai, diameter 20 cm	½ piece
Chappati, diameter 20 cm	1/3 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	1/3 cup
*Lentils	1/3 cup
(*Contains more protein than other foods in the list i.e. 5 g/serve)	
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
Waterchestnut	4 pieces
• 1 cup = 200 mL in volume = ¾ Chinese rice bowl (11.2 cm in diameter x 3.7 cm deep) • Tablespoon refers to dessert spoon level (equivalent to 2 teaspoons)	

- Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. [57 (Level III)]

APPENDIX 2: Food Groups and Exchange List *(cont.)*

Fruits (Each item contains 15 g carbohydrate and 60 calories)	
Fruits	
Orange	1 medium
Can be exchanged for	
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), dries	2 pieces
Raisin	20 g
Durian	2 medium seeds
Mango	½ small

- Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. [57 (Level III)]

APPENDIX 2: Food Groups and Exchange List *(cont.)*

Lean Meat, Fish and Meat Substitutes (Each serving of meat and substitutes contain 7 g of protein. These foods contain varying amounts of fat and energy, but negligible carbohydrate)				
	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 for	
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)				
	CHO (g)	**Protein (g)**	**Fat (g)**	**Energy (kcal)**
Skimmed (1% fat)	15	8	Trace	90
Low fat (2% fat)	12	8	5	125
Full cream	10	8	9	150

Milk	
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

- Adapted from Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013. [57 (Level III)]

APPENDIX 2: Food Groups and Exchange List *(cont.)*

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 for	
Butter, margarine	1 level teaspoon
Mayonnaise	
Shortening, lard	
Peanut butter (smooth or crunchy)	2 level teaspoons
Cream, unwhipped (heavy)	1 level tablespoon
Cream cheese	
Salad dressing	
Cream, unwhipped (light)	2 level tablespoons
Coconut, shredded	
Coconut milk (santan)	
Non dairy creamer, powder	
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 Type 2 Diabetes Mellitus, 2013. [57 (Level III)]

APPENDIX 3: Glycaemic Index of Foods [498-502 (Level III)]

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	Lasagne 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 Soy milk (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

APPENDIX 4: Assessment Prior to Intense Exercise

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

• Adapted from the American Diabetes Association Standards for Medical Care in Diabetes – 2015. [4 (Level III)]

APPENDIX 5: Grading of Physical Activities

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

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

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

- Adapted from American College of Sports Medicine Position Stand. Progression Models in Resistance Training for Healthy Adults, 2009. [503 (Level III)]

APPENDIX 6: Dosage of Anti-diabetic Agents in Renal Failure

Generic Name	Usual Dose	Dose Adjustment in Renal Failure		
		Mild (CKD 2) (GFR 60-89 ml/min)	Moderate (CKD 3) (GFR 30-59 ml/min)	Severe (CKD 4 & 5) (GFR <30 ml/min)
Biguanide§				
Metformin	500–1000 mg BD	50%	25%	Avoid
Sulphonylureas^				
Glibenclamide	5 mg OD–10 mg BD	Use with caution	Avoid	
Gliclazide	80 mg OD–160 mg BD	No dose adjustment		Avoid
Gliclazide MR	30–120 mg OD	No dose adjustment		≥15: No dose adjustment <15: Avoid
Glimepiride	1–4 mg OD	Initiate with 1 mg od		Avoid
Glipizide	2.5–15 mg OD	No dose adjustment		Avoid
Meglitinides				
Repaglinide	0.5–4 mg TDS	No dose adjustment		Initiate at 0.5 mg with meals
Nateglinide	60–120 mg TDS	No dose adjustment		Initiate at 60 mg with meals
Alpha-glucosidase Inhibitor				
Acarbose	25–100 mg TDS	50 - 100%		≥25: 50 - 100% <25: Avoid
Thiazolidinediones				
Rosiglitazone	4–8 mg OD	No dose adjustment		
Pioglitazone	15–45 mg OD	No dose adjustment		
DPP-4 Inhibitors				
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	
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		
Alogliptin	25 mg OD	25 mg od	12.5 mg od	6.25 mg od

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

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

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

* Modified from the Malaysian Clinical Practice Guidelines on Diabetic Nephropathy, 2004 and Clinical Practice Guidelines on Management of Chronic Kidney Disease in Adults. [280, 293 (Level III)]

APPENDIX 6: Dosage of Anti-diabetic Agents in Renal Failure *(cont.)*

Generic Name	Usual Dose	Dose Adjustment in Renal Failure		
		Mild (CKD 2) (GFR 60-89 ml/min)	**Moderate (CKD 3)** (GFR 30-59 ml/min)	**Severe (CKD 4 & 5)** (GFR <30 ml/min)
GLP-1 Receptor Agonists				
Exenatide	5 mcg BD x 1 month, then 10 mcg BD	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	0.6 mg OD x 1 week, then 1.2–1.8 mg OD	No dose adjustment	Limited data, use with caution	
Lixisenatide	10 mcg OD x 2 weeks, then 20 mcg OD	No dose adjustment	>50: No dose adjustment 30-50: Use with caution	Avoid
Dulaglutide	0.75–1.5 mg weekly	No dose adjustment		Use with caution
SGLT2 Inhibitors				
Dapagliflozin	5–10 mg OD	No dose adjustment	Avoid	
Canagliflozin	100–300 mg OD	No dose adjustment	45-60: 100 mg od <45: Avoid	Avoid
Empagliflozin	10–25 mg OD	No dose adjustment	45-60: 10 mg od <45: Avoid	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.				

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

- Modified from the Malaysian Clinical Practice Guidelines on Diabetic Nephropathy, 2004 and Clinical Practice Guidelines on Management of Chronic Kidney Disease in Adults. [280, 293] (Level III)

APPENDIX 7: The 5-Item Version of the International Index of Erectile Function [348 (Level III)]

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

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

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

Indeks Fungsi Seks Antarabangsa (IIEF-5) [349 (Level III)]

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

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

1. Bagaimanakah anda menentukan kadar keyakinan yang kemaluan anda berfungsi dan dapat mengekalkan ketegangannya.		Sangat rendah 1	Rendah 2	Sederhana 3	Tinggi 4	Sangat Tinggi 5
2. Apabila anda mengalami ketegangan zakar (kemaluan atau 'batang' keras) menerusi rangsangan seks, berapa kerap ketegangan itu cukup keras untuk persetubuhan?	Tiada Rangsangan seks 0	Langsung tidak pernah/hampir tidak pernah 1	Beberapa kali (kurang daripada 50%) 2	Kadang-kadang (kira-kira 50%) 3	Sering kali (lebih dari 50%) 4	Setiap kali/Hampir setiap kali 5
3. Sewaktu bersetubuh, berapa kerap anda dapat mengekalkan ketegangan kemaluan sehingga selesai persetubuhan?	Tidak mencuba persetubuhan 0	Langsung tidak pernah/hampir tidak pernah 1	Beberapa kali (kurang daripada 50%) 2	Kadang-kadang (kira-kira 50%) 3	Sering kali (lebih dari 50%) 4	Setiap kali/Hampir setiap kali 5
4. Sewaktu bersetubuh, berapa sukarkah untuk mengekalkan ketegangan kemaluan sehingga selesai persetubuhan?	Tidak mencuba persetubuhan 0	Tersangat sukar 1	Sangat sukar 2	Sukar 3	Sukar sedikit 4	Tidak sukar 5
5. Apabila anda cuba melakukan persetubuhan, berapa kerap anda berasa puas hati?	Tidak mencuba persetubuhan 0	Langsung tidak pernah/hampir tidak pernah 1	Beberapa kali (kurang daripada 50%) 2	Kadang-kadang (kira-kira 50%) 3	Sering kali (lebih dari 50%) 4	Setiap kali/Hampir setiap kali 5

1. Semua soalan, bermula dengan "Di sepanjang 4 minggu yang lalu"
2. Jumlahkan skor pada setiap item 1-5 (Jumlah skor yang mungkin = 25)
3. Klasifikasi Keterukan ED:

Jumlah skor	Classification
1-7	Sangat teruk
8-11	Sederhana
12-16	Ringan hingga sederhana
17-21	Ringan
22-25	Tidak ada masalah ED

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

Very high risk

• History of severe diabetes complications within 3 months prior to fasting:
  • Severe hypoglycaemia
  • Diabetic ketoacidosis
  • Hyperglycaemic hyperosmolar state
  • Recurrent hypoglycaemia

• Hypoglycaemia unawareness
• Type 1 diabetes
• Acute severe illness
• Sustained poor glycaemic control (A1c >9%)
• Performing intense physical labour
• Pregnancy
• Advanced renal failure / chronic haemodialysis
High risk
• Moderate hyperglycaemia (A1c 7.5–9.0%)
• Moderate renal failure
• Advanced macrovascular complications
• Living alone and treated with insulin or sulphonylureas
• Patients with comorbid conditions that present additional risk factors
• Old age with ill health
• Treatment with drugs that may affect mentation
Moderate risk
• Well-controlled diabetes treated with short-acting insulin secretagogues
Low risk
• Well-controlled diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, incretin-based therapies and/or SGLT2 inhibitors in otherwise healthy patients

- Adapted from "Recommendations for Management of Diabetes During Ramadan: Update 2010". Diabetes Care, 2010. [454 (Level III)]

***Note*:**

- This classification is based largely on expert opinion and not on scientific data derived from clinical studies.
- Those who fall in the "very high" and "high risk" group are advised to abstain from fasting.

GLOSSARY OF TERMS

A1c	Glycated Haemoglobin
ACEI	Angiotensin-converting Enzyme Inhibitor
ACR	Albumin-Creatinine ratio
ADA	American Diabetes Association
ADI	Acceptable daily intake
AGI	a-glucosidase inhibitor
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ARB	Angiotensin Receptor Blocker
BD	Twice daily (Bis Die)
BG	Blood glucose
BMI	Body Mass Index
BP	Blood Pressure
BUSE	Blood Urea And Serum Electrolytes
CAN	Cardiac autonomic neuropathy
CCB	Calcium Channel Blocker
CCF	Congestive Cardiac Failure
CCSI	Continuous subcutaneous insulin infusion
CCU	Coronary Care Unit
CGM	Continuous Glucose Monitoring
CHD	Coronary Heart Disease
CHO	Carbohydrate
CKD	Chronic Renal Disease
CVD	Cardiovascular Disease
DAN	Diabetic autonomic neuropathy
DCCT	Diabetes Control and Complications Trials
DHEA	Dehydroepiandrosterone
DKA	Diabetes Ketoacidosis
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DPN	Diabetic peripheral neuropathy
DPP-4i	Dipeptidyl peptidase-4 inhibitors
DR	Diabetic retinopathy
ECG	Electrocardiogram
ED	Erectile Dysfunction
ESRD	End stage renal disease
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration

FPG	Fasting Plasma Glucose
FRS	Framingham Risk Score
FSD	Female sexual disorder
FSFI	Female Sexual Function Index
GDM	Gestational Diabetes Mellitus
GFR	Glomerular filtration rate
GI	Glycaemic Index
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1 RA	Glucagon-like Peptide 1 Receptor Agonist
HDL	High Density Lipoprotein
HDU	High Dependency Unit
HHS	Hyperglycaemic Hyperosmolar Syndrome
ICU	Intensive Care Unit
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IIEF	International Index of Erectile Dysfunction
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
LAGB	Laproscopic Adjustable Gastric Banding
LBW	Low Birth Weight
LDL	Low Density Lipoprotein
LGA	Large for Gestational Age
LMWH	Low molecular weight heparin
LSCS	Lower Segment Caesarean Section
MADRAC	Malaysian Adverse Drug Reaction Advisory Committee
MDI	Multiple Daily Injection
MDRD	Modification of Diet in Renal Disease
MNT	Medical Nutrition Therapy
MRP	Meal replacement
NAFLD	Non-alcoholic Fatty Liver Disease
NCEP	National Cholesterol Education Program
NICE	National Institute for Health and Care Excellence
NPDR	Non-proliferative Diabetic Retinopathy
NPH	Neutral Protamine Hagedorn
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OAD	Oral Anti-diabetic
OD	Once Daily (Omni Die)
OGTT	Oral Glucose Tolerance Test
OM	On Morning (Omni Mane)
ON	On Night (Omni Nocte)

OSAS	Obstructive Sleep Apnoea Syndrome
PCOS	Polycystic Ovarian Syndrome
PDE-5	Phospodiesterase-5
PN	Parenteral nutrition
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PPAR-γ	Peroxisome Proliferator-Activated Receptor-Gamma
PPG	Post-prandial Plasma Glucose
RPG	Random Plasma Glucose
SBMG	Self Blood Monitoring Glucose
SC	Subcutaneous
SCORE	Systematic Coronary Risk Evaluation
SGA	Small for Gestational Age
SIADH	Syndrome of Inappropriate Antidiuretic Hormone
SSB	Sugar Sweetened Beverage
SSI	Sliding Scale Insulin
SSRI	Selective Serotonin Receptor Inhibitor
SU	Sulphonylurea
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TDD	Total daily dose
TDS	Three Times Daily (Ter Die Sumendus)
TG	Triglycerides
TZD	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	Vascular Endothelial Growth Factor
WC	Waist Circumference
WHO	World Health Organisation

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LEVELS OF EVIDENCE SCALE

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

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

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

GRADES OF RECOMMENDATIONS

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

Source: Modified From Scottish Intercollegiate Guidelines Network (SIGN)