CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION

Hyperglycaemia

- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Islet $\beta$-cell

Islet $\alpha$-cell

Impaired Insulin Secretion

2016
Facts about this edition of the CPG:

1. First in Asia to advocate A1c as a diagnostic tool to diagnose diabetes*

2. It’s among the first in the world to have a different A1c cut-off point (6.3%) for diabetes

3. First in the world to advocate 4 oral anti-diabetic agents before initiating insulin therapy (provided A1c < 10%)

4. First in the world to produce patient specific algorithm

5. Among the first in the world to offer GLP-1 RA as an alternative to initiating insulin therapy with basal insulin (provided A1c < 10%)

Other notable changes:

6. BP target for diabetes 135/75

7. Aspirin for primary prevention of CVD for those above 65 years of age

8. Universal screening for gestational diabetes

* The Japanese advocates A1c as a diagnostic test but it must be accompanied by FBG or oGTT from the same blood sample back in 2010.
## LIST OF CONTRIBUTORS

<table>
<thead>
<tr>
<th>Editor</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Nor Azmi Kamaruddin</td>
<td>Consultant Physician</td>
</tr>
<tr>
<td>Prof. Dr. Norlela Sukor</td>
<td>Universiti Sains Islam Malaysia</td>
</tr>
<tr>
<td>Dr. Ahmad Marzuki Omar</td>
<td>Nilai, Negeri Sembilan</td>
</tr>
<tr>
<td>Dr. Ooi Cheow Peng</td>
<td></td>
</tr>
<tr>
<td>Dr. Mohd Rahman Omar</td>
<td></td>
</tr>
</tbody>
</table>

### Editorial Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Chan Siew Pheng</td>
<td>Senior Consultant Endocrinologist</td>
</tr>
<tr>
<td>Sime Darby Medical Centre</td>
<td></td>
</tr>
<tr>
<td>Subang Jaya, Selangor</td>
<td></td>
</tr>
<tr>
<td>Prof. Dr. Winnie Chee Siew Swee</td>
<td>Consultant Dietitian</td>
</tr>
<tr>
<td>International Medical University</td>
<td></td>
</tr>
<tr>
<td>Kuala Lumpur</td>
<td></td>
</tr>
<tr>
<td>Dr. Feisul Idzwan Mustapha</td>
<td>Public Health Physician</td>
</tr>
<tr>
<td>Disease Control Division</td>
<td></td>
</tr>
<tr>
<td>Department of Public Health</td>
<td></td>
</tr>
<tr>
<td>Ministry of Health Malaysia, Putrajaya</td>
<td></td>
</tr>
<tr>
<td>Dr. Hew Fen Lee</td>
<td>Consultant Endocrinologist</td>
</tr>
<tr>
<td>Subang Jaya Medical Centre</td>
<td></td>
</tr>
<tr>
<td>Subang Jaya, Selangor</td>
<td></td>
</tr>
<tr>
<td>Prof. Dato’ Paduka Dr. Mafauzy Mohamed</td>
<td>Senior Consultant Endocrinologist</td>
</tr>
<tr>
<td>Universiti Sains Malaysia Hospital</td>
<td></td>
</tr>
<tr>
<td>Kubang Kerian, Kelantan</td>
<td></td>
</tr>
<tr>
<td>Dr. Masni Mohamad</td>
<td>Consultant Endocrinologist</td>
</tr>
<tr>
<td>Putrajaya Hospital</td>
<td></td>
</tr>
<tr>
<td>Putrajaya</td>
<td></td>
</tr>
<tr>
<td>Dr. Mastura Ismail</td>
<td>Consultant Family Medicine Specialist</td>
</tr>
<tr>
<td>Seremban 2 Health Clinic</td>
<td></td>
</tr>
<tr>
<td>Seremban, Negeri Sembilan</td>
<td></td>
</tr>
</tbody>
</table>
Three main issues confronted the Development Group when revising the Clinical Practice Guidelines (CPG) for the Management of Type 2 Diabetes Mellitus (T2DM). First was the issue of increasing prevalence of diabetes followed by the increasing percentage of silent or undiagnosed diabetes especially in the young and finally the poor state of glycaemic control in our patients.

Diagnosing T2DM with Fasting Blood Glucose (FBG) or oral Glucose Tolerance Test (oGTT) is fraud with problems. FBG and especially oGTT are very cumbersome. Based on the NHMS 2015 report, 9.2% of those above the age of 18 years did not know they have diabetes compared to a mere 8.2% who knew. This is worse in those below 30 years old where 88% of those with diabetes did not know they have the disease. Based on the Metabolic Syndrome Study of Malaysia data, an A1c of 6.3% produced a positive predictive value of 58% and negative predictive value of 84% with an ROC curve of 0.85 in diagnosing diabetes. This is also supported by the retinopathy study in neighbouring Singapore and data from mainland China and Hong Kong. By being one of the first few countries in Asia to utilise A1c as a diagnostic tool we hope to be able to bring down the number of undiagnosed diabetes in this country.

On the issue of poor glycaemic control several contributing factors come to mind; first and foremost is the issue of compliance to medications especially that to insulin. Two basic concerns underlie the problem of compliance, that of the fear of hypoglycaemia and weight gain. Hypoglycaemia as we come to understand is no more a one off phenomenon. It has long term repercussions. Patients who develop severe hypoglycaemia have a 20% chance of developing cardiovascular disease in the following year. Similarly, weight gain which tends to be associated with conventional therapies such as insulin secretagogues and insulin could very well explain our inability to improve cardiovascular outcomes when it comes to treating hyperglycaemia in diabetes. The treatment algorithm, follow-up algorithm and patient specific algorithm (which is a first for any CPG on T2DM) were tailored to minimise hypoglycaemia and the undesirable effect of weight gain.

Another important point that calls for our attention is the need to manage the various individual abnormalities that contribute to hyperglycaemia in diabetes. The Ominous Octet (its illustration is on the front cover of the CPG) has to be addressed if we are to make any headway in slowing the disease progression of diabetes. Tackling blood glucose alone is insufficient. Study by DeFronzo which initiated triple therapy with metformin, thiazolidinedione and GLIP-1 RA at the onset of diabetes was shown to be effective in slowing the progression of diabetes. Despite its publication in 2014, no guideline on T2DM has found it necessary to include such an approach in any of its treatment algorithms. Perhaps it is we, the diabetes caregiver or the newly-diagnosed patients who are overwhelmed by the idea of starting all three agents at the same time or even the health financing systems which are not ready for it. In this respect the CPG has taken a middle path by being the first in the world to allow the use of up to 4 anti-diabetic agents before initiating insulin therapy provided the A1c is below 10 %. Though it is a far cry from the triple therapy of De Fronzo, it still holds true to the spirit of treating the various pathologies that go wrong with diabetes by allowing up to 4 agents to try and correct if not all, at least some of these pathologies.

The CPG has also taken the brave stand by being the first to recommend GLIP-1 RA as an alternative to basal insulin in those who are about to be initiated with insulin therapy (provided the A1c is < 10 %). Despite most other CPGs advocating aspirin in those above the age of 40-50 years with high Framingham Risk scores based on multitude of meta-analysis and systematic analyses, we believe in the well tested principle that no amount of meta-analysis can outperform a well conducted RCT. Thus we are sticking our necks out with the JPAD Study, the only study on primary prevention with aspirin in diabetes which only advocates the anti-platelet in those above the age of 65 years. As recommended by WHO we also support universal screening for GDM with oGTT for all pregnant women though we acknowledged the scarcity of manpower and resources in some places.

Nor Azmi Kamaruddin
<table>
<thead>
<tr>
<th>Introduction</th>
<th>Overview of Type 2 Diabetes Mellitus &amp; Revised CPG for the Management of T2DM 2015</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topic 1</td>
<td>Screening &amp; Diagnosis</td>
<td>12</td>
</tr>
<tr>
<td>Topic 2</td>
<td>Targets For Control</td>
<td>26</td>
</tr>
<tr>
<td>Topic 3</td>
<td>Medical Nutrition Therapy &amp; Low Glycaemic Index Diet</td>
<td>44</td>
</tr>
<tr>
<td>Topic 4</td>
<td>Physical Activity</td>
<td>64</td>
</tr>
<tr>
<td>Topic 5</td>
<td>Oral Anti-Diabetic Medications</td>
<td>74</td>
</tr>
<tr>
<td>Topic 6</td>
<td>Insulin Therapy &amp; Injectables</td>
<td>96</td>
</tr>
<tr>
<td>Topic 7</td>
<td>Diabetes with Hypertension</td>
<td>114</td>
</tr>
<tr>
<td>Topic 8</td>
<td>Diabetes with Dyslipidaemia</td>
<td>128</td>
</tr>
<tr>
<td>Topic 9</td>
<td>Diabetes with Obesity</td>
<td>138</td>
</tr>
<tr>
<td>Topic 10</td>
<td>Management of Diabetic Emergencies 1</td>
<td>152</td>
</tr>
<tr>
<td>Topic 11</td>
<td>Management of Diabetic Emergencies 2</td>
<td>166</td>
</tr>
<tr>
<td>Topic 12</td>
<td>Management of Chronic Complications 1</td>
<td>187</td>
</tr>
<tr>
<td>Topic 13</td>
<td>Management of Chronic Complications 2</td>
<td>206</td>
</tr>
<tr>
<td>Topic 14</td>
<td>Diabetes in Special Populations 1</td>
<td>225</td>
</tr>
<tr>
<td>Topic 15</td>
<td>Diabetes in Special Populations 2</td>
<td>243</td>
</tr>
<tr>
<td>Topic 16</td>
<td>Diabetes in Special Populations 3</td>
<td>259</td>
</tr>
<tr>
<td>Topic 17</td>
<td>Prevention of Type 2 Diabetes Mellitus</td>
<td>274</td>
</tr>
<tr>
<td>Appendix 1</td>
<td>Template for Training Program</td>
<td>283</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>Pre-test and Post-Test Questionnaire</td>
<td>286</td>
</tr>
</tbody>
</table>
INTRODUCTION

The Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (5th Edition) was published in December 2015. This Training Manual is produced to assist ‘trainers’ in delivering all of the components relating to the implementation of the new CPG systematically and effectively.

This document contains the following:
1. CD-ROM containing the PowerPoint presentations
2. The outline for each topic
3. Case studies at the end of each topic
4. Template for the training program/schedule
5. Pre-test and post-test questionnaire

Target audience:
All healthcare providers involved with the care of diabetes patients in both primary healthcare and secondary healthcare settings.

Table 1: Summary of Training Manual Content

<table>
<thead>
<tr>
<th>No.</th>
<th>Topic</th>
<th>Duration (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lecture</td>
</tr>
<tr>
<td>1.</td>
<td>Overview of Type 2 Diabetes Mellitus &amp; Revised CPG for the Management of T2DM 2015</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Screening &amp; Diagnosis</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Target for Control</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Medical Nutrition Therapy &amp; Low Glycaemic Index Diet</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Physical Activity</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Oral Anti-Diabetic Medications</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Insulin Therapy &amp; Injectables</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Diabetes with Hypertension</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Diabetes with Dyslipidaemia</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Diabetes with Obesity</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Management of Diabetic Emergencies - Hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Management of Diabetic Emergencies – DKA &amp; HHS</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Management of Chronic Complications 1</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Management of Chronic Complications 2</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Diabetes in Pregnancy</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Diabetes in Ramadan</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Diabetes in Adolescents</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Prevention of Type 2 Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>
overview of type 2 diabetes mellitus & revise cpg for the management of T2DM 2015
The NHMS 2015 data are quoted above instead of the NHMS 2011 which was used in the CPG.

**Diabetes: The Disease**

- 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 dermalopathy.
- Currently there is no known cure but the disease can be controlled enabling the individual to have an improved quality of life.
- The main aim of management is directed at reducing acute and chronic complications (microvascular and macrovascular).

The NHMS 2015 data are quoted above instead of the NHMS 2011 which was used in the CPG.

**Diabetes: The Burden**

- The National Health and Morbidity Survey (NHMS) 2015 reported diabetes prevalence figures of 17.5% for adults above the age of 18 years.
- Among adults above the age of 18 years old, the prevalence was highest in the Indians (22.1%) followed by Malays (14.6%) and Chinese (12.0%).
- Of concern, 53% 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 (67%) followed by Chinese (64%) and Indians (53%).
- Similarly the proportion of undiagnosed diabetes is also highest in the young.
Based on the classification from the Malaysian Clinical Practice Guidelines of Obesity (2004), BMI was classified into 6 categories; underweight (<18.50 kg/m$^2$), normal (18.50 - 22.99 kg/m$^2$), overweight (23.00 - 27.49 kg/m$^2$), obese I (27.50 - 34.99 kg/m$^2$), obese II (35.00 - 39.99) and obese III (>40 kg/m$^2$). The World Health Organization (1998) classified body mass Index (BMI) into 6 categories; underweight (<18.5 kg/m$^2$), normal (18.5-24.99 kg/m$^2$), overweight (25.0-29.99 kg/m$^2$), obese I (30.34-34.99 kg/m$^2$), obese II (35.39-39.99) and obese III (>40 kg/m$^2$).

**SLIDE 7**

Type 2 diabetes increases CVD risk

People with type 2 diabetes have a higher risk of CVD events relative to people without diabetes.

- In the Framingham Heart Study, diabetes predisposed subjects to all of the major atherosclerotic diseases. CHD was the most common and most lethal.
- The chart shows the age-adjusted relative risk of CVD for diabetics versus non-diabetics (16-year follow-up after the tenth biennial examination of the Framingham Cohort Study). It is based on 554 men (46 with diabetes) and 760 women (43 with diabetes) who were free of CVD at examination.
- The risk for individuals without diabetes is represented by the line at a risk ratio of one. The risk of CVD is greater for those with diabetes compared with those without.

The mortality rate in men with diabetes is twice as great as that in patients without diabetes.

The 20-year mortality of the men aged 44–55 years in the Whitehall, Paris Prospective and Helsinki Policemen studies was analysed.

75% of the deaths in the Helsinki study were from CVD, compared with 56% in Whitehall and 31% in France.

In each study, the mortality rate from all causes was found to be twice as great in patients with diabetes.

Diabetes was associated with an increased non-cardiovascular mortality in addition to excess cardiovascular mortality.


Better Control Equals Reduced Risk of Complications

The UKPDS has proven beyond doubt that intensive glycaemic control is strongly associated with real clinical benefits for patients with type 2 diabetes.
UKPDS 35 was a prospective observational study to determine the relation between exposure to hyperglycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes who were participants in the UKPDS.

In this sub-analysis, 3642 white, Asian Indian and Afro-Caribbean patients had HbA$_1c$ measured 3 months after their diabetes diagnosis. The sub-analysis included complete data for potential confounders.

Every 1% decrease in HbA$_1c$ was associated with clinically important reductions in the incidence of
- diabetes-related death (↓21%)
- myocardial infarction (↓14%)
- microvascular complications (↓37%)
- peripheral vascular disease (↓43%)

There is no lower limit beyond which reductions in HbA$_1c$ cease to be of benefit. Taking diabetes-related death as an example, this means that:
- a reduction in HbA$_1c$ of 2% delivers a 42% reduction in risk
- a reduction in HbA$_1c$ of 3% delivers a 63% reduction in risk
- and so on.

Therefore, the greater the reduction in HbA$_1c$, the greater the protection against complications.

**Slide 14**

**DiabCare Malaysia 2008 vs 2013: Blood glucose values**

![Graph showing blood glucose values](image)

Similar HbA1c and FPG but slightly lower PPG values in 2013 vs 2008

**Slide 15**

**Asian Countries Diabetes Complications**

**Coronary Heart Disease & Strokes 2008**

<table>
<thead>
<tr>
<th>Country</th>
<th>Indonesia (%)</th>
<th>Bangladesh (%)</th>
<th>Singapore (%)</th>
<th>Malaysia (%)</th>
<th>Taiwan (%)</th>
<th>Thailand (%)</th>
<th>Philippines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>10.1</td>
<td>6.6</td>
<td>6.3</td>
<td>19.3</td>
<td>4.7</td>
<td>5.1</td>
<td>10.1</td>
</tr>
<tr>
<td>Heart attacks</td>
<td>5.7</td>
<td>5.3</td>
<td>3.2</td>
<td>12.4</td>
<td>3</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Coronary occlusion</td>
<td>1.7</td>
<td>1.4</td>
<td>6.3</td>
<td>13.1</td>
<td>4.6</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.8</td>
<td>2.2</td>
<td>4.6</td>
<td>7.2</td>
<td>4.5</td>
<td>4.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>


**Slide 16**

**What are the main changes in 2015?**

**Management of Type 2 Diabetes Mellitus**

CLINICAL PRACTICE GUIDELINES

[Image showing main changes in management]
What are the (10) main changes in 2015?

1. Addition of 8 new sections
   a) New oral agent
   b) Algorithms for FU & Specific Patient Profiles
   c) Table of efficacy, AE of Anti Diabetic Agents
   d) Acute diabetic emergencies ie Hypo, DKAs, HHS
   e) Mix of elderly, adolescents, obese, Ramadan
   f) Male & Female Sexual Dysfunction
   g) Mental Health
   h) Unproven therapies incl TCM
2. A1c as a diagnostic tool for T2DM
3. A1c above 6.3% diagnostic of T2DM
4. A1c target of 6.5% consolidated with ADVANCE Trial
5. BP target of 135/75 based on ADVANCE-BP arm
6. 3 or 4 OADs before insulin if A1c < 10.0%
7. Second line for LDL-lowering (IMPROVE-IT)
8. CVD risk estimate for target intensification NOT for cardiovascular work-up (BAAD Study)
9. Primary prevention with aspirin only in those above 65 years old (JPAD Study)
10. Hyperglycaemia in Pregnancy (GDM & T2DM)
Algorithm B: Management of T2DM with Hyperglycaemic Hyperosmolar State

**PROTOCOL FOR MANAGEMENT OF ADULTS PATIENTS WITH HYPERGLYCAEMIC HYPEROSMOLAR STATE (HHHS)**

- **History**: Ask about recent events, medications, diet, alcohol, infections, recent surgery, travel, recent stress.
- **Examination**: Vital signs, physical examination, neurological examination, mental status.
- **Investigations**: FBC, U&Es, LFTs, renal function tests, ECG, chest X-ray, CT scan, MRI, electrolytes, osmolality, blood glucose, sodium, potassium.

**3-prong approach to the management of Hyperglycaemic Hyperosmolar State**

1. Hydration
2. Ketone bodies
3. Hyperglycaemia


**Effective serum osmolality calculation:** si units: (3Hct + 2K + Glucose + Urea (in mmol/L))

**Serum Na** should be corrected for hyperglycaemia (si units: Corrected serum sodium = Measured serum sodium - (Glucose measured - 5.5) x .24, all in mmol/L).

---

**Slide 24**

Clinical practice guidelines aim to help physicians and patients reach the best healthcare decisions.

Steinbrook R, NEJM 2007

Thank you
screening and diagnosis
Screening & Diagnosis

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

Strategy
- Screening the general population for at risk individuals.
- Screening of specific high-risk populations.
Who should be screened?

Symptomatic Individuals

Symptoms & Signs

- Polyuria
- Polydipsia
- Weight loss
- Lethargy
- Tiredness
- Blurred Vision
- Boils/abscesses
- Pruritus Vulvae
- DKA
- Retinopathy
- Nephropathy
- Neuropathy
- Foot ulcers/gangrene
- Angina/Ml/CVA

Who should be screened?:
Asymptomatic

- Screening should begin at age ≥ 30 years.
Who should be screened?
Asymptomatic

- Adults who are overweight or obese (by BMI or waist circumference), and have one or more of the following additional risk factors:
  - First degree relative with diabetes
  - History of CVD
  - Hypertension
  - IGT or IFG
  - Abnormal HDL or TG
  - Other clinical conditions associated with insulin resistance
  - Women who delivered a baby weighing >4 kg, or had GDM
  - Women with PCOS
  - Physical inactivity
  - Special populations (e.g., those on ARV therapy or atypical antipsychotic drugs)

Note: In those without these risk factors, testing should begin at the age of 30 years. If normal, repeat annually.

Prevalence of Diabetes, ≥18 years, by age groups (2015)

Screening Test

- Screening can be done by measuring either venous or capillary blood using glucometer.
- Tests that can be performed are HbA1c, OGTT, FPG or RPG.
SLIDE 10

Algorithm 1: Screening for T2D in Symptomatic Individuals

WITH SYMPTOMS

Venous Plasma Glucose

Fasting

<7.0

≥7.0

≥11.1

<11.1

OUT

Random

Type 2 Diabetes Mellitus

SLIDE 11

Algorithm 2: Screening for T2DM in Asymptomatic Individuals

ASYMPTOMATIC WITHOUT RISK

Capillary Random Blood Glucose

<5.6

≥5.6

Venous FPG

<6.1

6.1 - 6.9

≥7.0

Vennous FPG

NORMAL

Second FPG

<7.0

≥7.0

NORMAL

OGTT

≥11.1

OUT

DM

SLIDE 12

DM Diagnostic Criteria

Criteria For Diabetes Diagnosis

1. A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCC assay.

2. FPG ≥ 7.0 mmol/l. Fasting is defined as no caloric intake for at least 8 hr.

3. 2-hr plasma glucose ≥ 11.1 mmol/l during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 11.1 mmol/l.

5. Any of 4 but 1-3 should be confirmed by repeat testing.

Diabetes Care January 2010 vol. 33 no. Supplement 1 S02-S09
**Diagnosis: Diabetes Mellitus**

1. Symptoms of diabetes (polydipsia, polyuria, unexplained weight loss) PLUS a random plasma glucose > 11.1 mmol/L
   or
2. Fasting plasma glucose > 7.0 mmol/L after overnight (at least 8 hours) fast
   or
3. Two-hour plasma glucose > 11.1 mmol/L during a standard 75g oral glucose tolerance test
   or
   The A1c test should be performed in a laboratory using a method that is NGSP certified and standardised to the DCCT assay.

   Any of these criteria establishes the diagnosis however FPG & OGTT needs to be confirmed on a later day if asymptomatic.

**Diagnostic values – A1c**

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

- These values are based on currently available data for Malaysia.
- For a precise classification of pre-diabetes, an OGTT is recommended.
- 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.
While A1c is an excellent measure for diagnosis, it is essential to know conditions where the value may not adequately reflect true glycemic control and other measures such as fasting blood sugar or OGTT may be more helpful.
Important conditions where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status.

This includes common conditions such as B12 and Fe deficiency that can falsely increase A1c and also increased red cell turnover states and factors that increase erthropoiesis such as use of EPO, Fe, B12 deficiency – which can falsely lower A1c.

So, while A1c is convenient for patients understanding the factors that affect the accuracy of it’s ability to diagnose diabetes.

While all 3 approaches predict microvascular disease and can be used for diagnosis, A1c may be a better predictor of macrovascular disease. The decision of which test to use for diabetes diagnosis is left to clinical judgment. Each diagnostic test has advantages and disadvantages

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>Established standard, Fast and easy, Single Sample</td>
<td>Sample not stable, Day-to-day variability, Inconvenient to fast glucose homeostasis in single time point</td>
</tr>
<tr>
<td>2hPG in 75 g OGTT</td>
<td>Established standard</td>
<td>Sample not stable, Day-to-day variability, Inconvenient, Unpalatable, Cost</td>
</tr>
<tr>
<td>A1C</td>
<td>Convenient, Single sample, Low day-to-day variability, Reflects long term [glucose]</td>
<td>Cost, Affected by haemoglobinopathies, Standardised, validated assay required, Not used for age &lt;18, pregnant women or suspected T1DM</td>
</tr>
</tbody>
</table>

Advantages and disadvantage of assays for glucose and HbA1c

<table>
<thead>
<tr>
<th>Test</th>
<th>Glucose</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient preparation prior to collection of blood</td>
<td>Stringent requirements if measured for diagnostic purposes</td>
<td>None.</td>
</tr>
<tr>
<td>Processing of blood</td>
<td>Stringent requirements for rapid processing, separation and storage of plasma or serum minimally at 4°C</td>
<td>Avoid conditions for more than 12h at temperatures &gt;20°C. Otherwise keep at 4°C (stability minimally 1 week)</td>
</tr>
<tr>
<td>Measurement</td>
<td>Widely available</td>
<td>Not readily available worldwide</td>
</tr>
<tr>
<td>Standardization</td>
<td>Standardised to reference method procedures</td>
<td>Standardised to reference method procedures</td>
</tr>
<tr>
<td>Routine calibration</td>
<td>Adequate</td>
<td>Adequate</td>
</tr>
<tr>
<td>Interferences: illness</td>
<td>Severe illness may increase glucose concentration.</td>
<td>Severe illness may shorten red cell life and artificially reduce HbA1c values.</td>
</tr>
<tr>
<td>Haemoglobinopathies</td>
<td>Little problem unless the patient is ill.</td>
<td>May interfere with measurement in some assays.</td>
</tr>
<tr>
<td>Haemoglobinopathy traits</td>
<td>No problems.</td>
<td>Most assays are not affected.</td>
</tr>
<tr>
<td>Affordability</td>
<td>Affordable in most low and middle income country settings.</td>
<td>Unaffordable in most low and middle-income country settings.</td>
</tr>
</tbody>
</table>

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

TRAINING MANUAL FOR HEALTHCARE PROFESSIONALS
MANAGEMENT OF TYPE 2 DIABETES MELLITUS
(5th Edition)

SLIDE 21

Advantages and disadvantages of various HbA1c assay methods

<table>
<thead>
<tr>
<th>Assay</th>
<th>Principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion Exchange Chromatography</td>
<td>HbA1c has lower isoelectric point and migrates faster than other Hb components.</td>
<td>Can impact chromatograms for Hb variants. Measurements with great precision.</td>
<td>Validates interference from haemoglobinopathies, and slightly carboxylated Hb but the current see exchange assays correct for HbF and carboxylated Hb. Does not interfere.</td>
</tr>
<tr>
<td>Boronate Affinity</td>
<td>Glucose binds to α-amino phenylboronic acid.</td>
<td>Minimal interference from haemoglobinopathies, HbF and carboxylated Hb.</td>
<td>Measures not only glutamic α-terminal valine on β chain, but also β chain and other α chains of glycation is chains. May be affected by haemoglobinopathies with altered amino-terminal α chain formation resistant to Hbf.</td>
</tr>
<tr>
<td>Immunoassays</td>
<td>Antibody binds to glucose and telomer 4 α-carboxylic acids on β chain.</td>
<td>Not affected by Hbc, HbA2 or carboxylated Hb. Relative ease to interpret under many different formats.</td>
<td></td>
</tr>
</tbody>
</table>

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

SLIDE 22

SLIDE 23

Cardiovascular Risk Estimation

- People with pre-diabetes and T2DM are at high risk of CVD
  - 2-3 fold increased risk of developing CVD
  - 60% of patients with T2DM will die from CVD
- Therefore, CV profiles should be determined at diagnosis
- Two tools recommended for CV risk assessment:
  - Framingham Risk Score (FRS)
  - Systematic Coronary Risk Evaluation (SCORE) – high model
- Those who are in the high-risk group should be treated aggressively with closer monitoring.
Recommendations

1. Screening for diabetes using FPG or A1c should be performed annually in those with risk factors and those ≥30 years.

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.

3. Testing with a 75-g OGTT should be considered in individuals with a FPG of ≥8.1 to 6.9 mmol/L or A1c between 5.6 to 6.2% in order to identify individuals with IGT or diabetes.

4. Diagnosis of diabetes and pre-diabetes can be made using fasting glucose, random glucose, OGTT or A1c.

5. At diagnosis of pre-diabetes and diabetes, it is recommended to perform cardiovascular risk assessment using either FRS or SCORE-high model.
Case Study

screening and
diagnosis
**Case 1**

Mrs. VN is a 40-year-old housewife.

She has hypertension, on treatment at a private GP. She says that it is well controlled on medication (not sure of the name of the tablet).

Her BMI is 32 kg/m², and the doctor has been advising her to lose weight.

Her mother and elder sister both have diabetes.

She doesn’t smoke or drink but likes sweet cakes and carbonated drinks.

---

**SLIDE 2**

1. Will you screen her for diabetes?
   - Yes
   - No

2. What test(s) will you use?

3. What are her current risk factors?
   - Age
   - Sedentary lifestyle (possibly – most housewives have quite sedentary lifestyle)
   - Unhealthy diet
   - Obese
   - Hypertension
   - Positive family history

She requires screening. Asymptomatic individual.

---

**SLIDE 3**

**Initial investigation**

OGTT:
- FBS: 5.4 mmol/L
- 2-hour: 9.4 mmol/L
Diagnosis and action plan

What is the diagnosis?
- Impaired glucose tolerance.

Do you need to do any additional test(s) to confirm diagnosis?
- No need additional test to confirm IGT.

What is her risk for developing cardiovascular disease?
- Use a CV risk calculator to assess risk (e.g. Framingham Risk Score or SCORE-high model)

Case 2

Mrs. HR is a 48-year-old lecturer whom you have screened for diabetes since she is over 40, and has a family history of diabetes.

You decide to use the A1C test for a change as she is complaining about the OGTT and the fact that she has to fast every screening visits. She also thought the glucose drink is just too much.

Her first A1C comes back as 6.3%.

Case 2

What is your next course of action?

A. Tell her she has DM
B. Tell her she has prediabetes
C. Ask her to repeat the A1c test in 3 months’ time
D. Ask her to repeat the A1c test the following day or as soon as possible.
E. Ask her to do either a Fasting Blood Glucose Test or an OGTT.
Mrs. HR’s first result is in the diabetes range.

However, after reading the 2016 ADA guidelines which advocates repeat confirmatory laboratory test the following day, she decides to go for a repeat A1C the next morning.

Her next A1C is 6.5%.

Comment:

The diagnosis of Type 2 Diabetes should not be made unless a repeat A1c is performed 1 month later, as per M’sian CPG for T2DM 2015.

However she is at liberty to perform other blood glucose tests such as FBG or OGTT to confirm the diagnosis.
targets for control
SLIDE 1

Causes of Death in People With Diabetes

- 65% of Diabetic Patients Deaths are from CV Causes


SLIDE 2

UKPDS and myocardial infarction

- Conventional
- Intensive
  p=0.06

% of patients with MI

Risk reduction 16%
(CI 95%: 0-29%)

Years after randomisation

UKPDS 33 Lancet. 1999;352:837-863

SLIDE 3

Improved Glycemic Control and Diabetes Complications from UKPDS

- Decrease in risk of any diabetes-related end point (P<.0001)
- Decrease in risk of MI (P<.0001)
- Decrease in risk of stroke (P=0.04)
- Decrease in risk of microvascular complications (P<.0001)

**All-cause Mortality Hazard Ratio**

Intensive (SU/ins) vs. Conventional glucose control

<table>
<thead>
<tr>
<th>Number of events</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con.</td>
<td>213</td>
<td>267</td>
<td>330</td>
<td>400</td>
<td>460</td>
<td>537</td>
</tr>
<tr>
<td>Int.</td>
<td>489</td>
<td>810</td>
<td>737</td>
<td>866</td>
<td>1028</td>
<td>1163</td>
</tr>
</tbody>
</table>

HR = 0.87  
*p* = 0.006  
(5% CI)

**UKPDS: Legacy Effect of Earlier Glucose Control**

After median 6.5 years post-trial follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td><em>P</em>: 0.029</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 20%</td>
<td>24%</td>
</tr>
<tr>
<td><em>P</em>: 0.0009</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>13%</td>
</tr>
<tr>
<td><em>P</em>: 0.052</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td><em>P</em>: 0.44</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction; *P* = Log Rank


**Glucose lowering?**

1. The presence of a legacy effect argues for early intensive glucose lowering
2. Target HbA1c to 6.5% except where this requires complex treatment regimens or life expectancy is less than 5 years
Question 1: Does treatment-directed lowering HbA1c (below 6.0 to 6.5%) reduce CV endpoints?

UKPDS p UKPDS p
ACCORD 1.5
ADVANCE 1.2
VADT 1.5

After nearly 10 years of follow-up, patients with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy, but no improvement was seen in the rate of overall survival.


P: primary prevention;  S: secondary prevention

---

**Early vs Late Glycemic Intervention**

<table>
<thead>
<tr>
<th>Study</th>
<th>UKPDSb (N=3867)</th>
<th>ADVANCEb (N=11,140)</th>
<th>ACCORDb (N=10,251)</th>
<th>VADTb (N=1791)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes, y</td>
<td>0*</td>
<td>8</td>
<td>10</td>
<td>11.5</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>53</td>
<td>66</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Mean baseline HbA1c, %</td>
<td>7.1</td>
<td>7.5</td>
<td>8.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Mean baseline FPG, mmol/L</td>
<td>8.0</td>
<td>8.5</td>
<td>9.7</td>
<td>11.4</td>
</tr>
<tr>
<td>ΔHbA1c, %</td>
<td><strong>0.9</strong></td>
<td><strong>0.7</strong></td>
<td><strong>1.1</strong></td>
<td><strong>1.5</strong></td>
</tr>
<tr>
<td>CVD</td>
<td>&lt;&lt; ↓</td>
<td>&lt;&lt;</td>
<td>&lt;&lt;</td>
<td>↔ ↓</td>
</tr>
<tr>
<td>Mortality</td>
<td>↔ ↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

*Newly diagnosed patients with no previous history of CVD.


---

**Impact of Intensive vs Conventional Glycemic-Lowering Strategies on Risk of CV Outcomes Is Unclear**

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetes Duration (mean)</th>
<th>Anti-hyperglycemic Medication</th>
<th>Follow-up (median)</th>
<th>A1C: Between-arm Difference</th>
<th>Microvasc CVD</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCED</td>
<td>8 years</td>
<td>Intensive glucose control including glitazones vs standard treatment</td>
<td>5 years</td>
<td>7.5% (both arms)</td>
<td>-0.8%</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>ACCORDb</td>
<td>10 years</td>
<td>Multiple drugs in both arms</td>
<td>3.5 years</td>
<td>8.1% (both arms)</td>
<td>-1.1%</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>VADTb</td>
<td>11.5 years</td>
<td>Multiple drugs in both arms</td>
<td>5.6 years</td>
<td>9.4% (both arms)</td>
<td>-1.5%</td>
<td>↓</td>
<td>↔</td>
</tr>
</tbody>
</table>

---

Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) was a study of 11,140 patients randomized to receive intensive glucose control (HbA1c target ≤6.5%) with addition of gliclazide (or substitution of...
gliclazide for other sulfonylurea therapy) or standard glucose control (HbA1c target defined by local guidelines).

Patients in the standard treatment group who were receiving gliclazide when they entered the study substituted this drug with another sulfonylurea. At the end of the follow-up period, mean HbA1c values were 6.5% in the intensive-control group and 7.3% in the standard-control group (–0.8% between-arm difference). Intensive control resulted in a reduced risk for major microvascular events (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.77–0.97; \( P = 0.01 \)) but not for major macrovascular events (HR 0.94, 95% CI 0.84–1.06; \( P = 0.32 \)) or death from any cause (HR 0.93, 95% CI 0.83–1.06; \( P = 0.28 \)), including death from cardiovascular (CV) causes.\(^3\)

Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a randomized multicenter study that investigated the incidence of cardiovascular events among 10,251 diabetic patients receiving multiple antihyperglycemic medications as intensive therapy (target HbA1c <6%) vs standard therapy (target HbA1c 7.0–7.9%). An absolute between-treatment difference in HbA1c levels of –1.1% was observed in favor of the intensive therapy group.\(^4\) Intensive therapy did not significantly affect advanced measures of microvascular outcomes but did delay the onset of albuminuria and some measures of eye complications and neuropathy.\(^5\) The trial reported no significant differences in the rate of nonfatal stroke (HR 1.06, 95% CI 0.75–1.50; \( P = 0.74 \)) but found a significant reduction in incidence of nonfatal MI in the intensive-therapy group (HR 0.76, 95% CI 0.62–0.92; \( P = 0.004 \)). A concomitant increase in CV deaths (HR 1.35, 95% CI 1.04–1.76; \( P = 0.02 \)) and all-cause mortality (HR 1.22, 95% CI 1.01–1.46; \( P = 0.04 \)) in this group led to its early termination in 2008, 17 months before the study conclusion.\(^4\)

The Veterans Affairs Diabetes Trial (VADT), conducted in 1,791 veterans with poorly controlled T2DM, was designed to achieve an overall difference of –1.5% between intensive and standard glucose therapy arms. Microvascular complications were minimally affected by intensive glucose control, as no significant differences in retinopathy, major nephropathy, or neuropathy were seen. A nominally significant reduction (\( P = 0.05 \)) in any worsening of albumin excretion was observed in the intensive-therapy group. No significant differences were observed between the 2 groups in the incidence of major CV events (HR 0.88, 95% CI 0.74–1.05; \( P = 0.14 \)) or death from any cause (HR 1.07, 95% CI 0.81–1.42; \( P = 0.62 \)).\(^6\)
Main Point: Highlight the importance of a therapy that addresses this glucose triad, even at insulin initiation.

As FPG and postprandial plasma glucose (PPG) contribute to varying degrees at differing HbA1c levels, a treatment plan that addresses all three components of the “glucose triad” will be most effective. Targeting FPG and PPG will have a combined effect of lowering HbA1c, which has been clearly associated with lowering risks of future complications.

Reference:
As Patients Get Closer to A1C Goal, the Need to Successfully Manage PPG Significantly Increases

Postprandial glycemic excursions become more predominant in patients with good control of fasting plasma glucose. Therefore, treatment should focus on both FPG and PPG excursions in order to reach and maintain A1C targets.

Adapted from Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of Type 2 diabetic patients: variations with increasing levels of HBA(1c). *Diabetes Care*. 2003;26:881-885.

---

**Contribution of FPG and PPG to A1c**

- Landmark study using 4-point glucose measurement (290 T2DM subjects)
- PPG accounted for ~70% overall glycaemic exposure when A1c is low (<7.3%)
- Contribution from the fasting hyperglycaemia increasing as A1c increases
- With A1c >10.2%, contributions reversed;
  - PPG contributed ~30% and FPG ~70%

This analysis was based on 1-day, four-point daytime glucose profiles from 290 patients with type 2 diabetes who were treated with diet therapy with or without oral antihyperglycemic drug (OAD) therapy and without insulin. The findings suggested that PPHG accounted for ~70% of overall glycemic exposure above normal levels in patients in the lowest range of A1C (<7.3%), with the contribution from BHG increasing with higher A1C. In the highest A1C range (A1C >10.2%), the contributions were reversed; PPHG contributed ~30% and BHG ~70%.
The Steno-2 study showed the effect of a multiple risk factor intervention strategy in 160 subjects with type 2 diabetes with microalbuminuria. Although all these subjects had type 2 diabetes, the results suggest that multiple risk factor intervention may also be highly beneficial in subjects with the metabolic syndrome. Subjects in the intensive therapy group were to follow a reduced-fat diet and exercise regularly, offered smoking cessation counseling, prescribed an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II–receptor blocker (ARB) regardless of blood pressure, and received vitamin supplementation and aspirin; stepwise antiglycemic and antihypertension medications were also prescribed as well as lipid-modifying therapy with a statin and/or fibrate. Subjects receiving intensive therapy were much more likely to reach their total cholesterol goal (<175 mg/dL) and systolic blood pressure goal (<130 mm Hg) and to routinely use ACE inhibitors or ARBs (data not shown). Note that it was much more difficult to achieve systolic blood pressure goal than diastolic blood pressure goal. The difference between intensive and conventional therapy for hemoglobin A1c (glycosylated hemoglobin) was only 0.6%.

Reference:
Steno-2 follow up primary endpoint

In Steno-2, the intensive therapy group had a 53% reduction in macrovascular disease, relative to the conventional therapy group. This 53% reduction in macrovascular disease is much higher than the percent reduction reported in single intervention trials of blood pressure, lipids, or ACE inhibitors, suggesting that multiple risk factor interventions are critical in high-risk subjects.

Reference:

Composite endpoint of death from CV causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation, or surgery for PAD: Steno-2

In Steno-2, the intensive therapy group had a 53% reduction in macrovascular disease, relative to the conventional therapy group. This 53% reduction in macrovascular disease is much higher than the percent reduction reported in single intervention trials of blood pressure, lipids, or ACE inhibitors, suggesting that multiple risk factor interventions are critical in high-risk subjects.

Reference:
Figure 2. Changes in Selected Risk Factors during the Interventional Study and Follow-up Period. Panel A shows mean (±SE) values for selected risk factors during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines). In the conventional-therapy group, mean values were obtained at baseline, at 3.8 years, at 7.8 years, and at 13.3 years. At these intervals, the total numbers of patients in both study groups were 160, 149, 130, and 93, respectively. Panel B shows the percentage of patients in each group in whom the treatment goals for the intensive-therapy group were reached at the end of the study. Only one patient (in the intensive-therapy group) reached all five treatment goals at the end of follow-up. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. LDL denotes low-density lipoprotein.
**SLIDE 23**

**Treating the ABCs Reduces Diabetic Complications**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose control</td>
<td>Heart attack</td>
<td>↓37%¹</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>↓61%²</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Heart failure</td>
<td>↓56%³</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>↓44%³</td>
</tr>
<tr>
<td></td>
<td>Diabetes-related deaths</td>
<td>↓32%³</td>
</tr>
<tr>
<td>Lipid control</td>
<td>Coronary heart disease mortality</td>
<td>↓36%⁴</td>
</tr>
<tr>
<td></td>
<td>Major coronary heart disease event</td>
<td>↓55%⁵</td>
</tr>
<tr>
<td></td>
<td>Any atherosclerotic event</td>
<td>↓37%⁶</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease event</td>
<td>↓63%⁶</td>
</tr>
</tbody>
</table>

¹UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843
²UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843
³UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843
⁴UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843
⁵UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843
⁶UNP05 Study Group (UNP05 203). Lancet. 1986;322:837-843

**SLIDE 24**

**Glucose lowering – waste of time?**

- Glucose lowering, started early, may have long term cardiovascular benefits
- Multifactorial risk reduction is imperative

**SLIDE 25**

**Self-monitoring of Blood Glucose (SMBG)**

**Noninsulin Users**
- Introduce at diagnosis
- Personalize frequency of testing
- Use SMBG results to inform decisions about whether to target HbA1c or PPG for any individual patient

**Testing positively affects glycemia in T2D when the results are used to:**
- Modify behavior
- Modify pharmacologic treatment

**Insulin Users**
- All patients using insulin should test glucose
  - 2 times daily
  - Before any injection of insulin
  - More frequent SMBG (after meals or in the middle of the night) may be required
- Frequent hypoglycemia
- Not at A1C target
Targets for Control

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

- Modified from the NICE guideline: Type 2 diabetes: The management of type 2 diabetes, 2009. Glycaemic target should be individualised to minimise risk of hypoglycaemia. The committee acknowledges the increased CVD death in the intensive group of the ACCORD study. 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.

- 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.

- 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.
Case Study

targets for control
This case illustrates a newly diagnosed diabetes, with no end organ complications.

Still not able to do exercise or taking care of his diet because of the busy schedule.

Investigation results:
- A1c: 7.5%
- FBS: 5.4 mmol/L
- Se Creatinine: 64 μmol/L
- Triglycerides: 1.04 mmol/L
- T-cholesterol: 4.27 mmol/L
- HDL-C: 1.22 mmol/L
- LDL-C: 2.11 mmol/L

The A1c is still not within target of ≤ 6.5%. Other issues to address like obesity, diet and compliance before uptitrating the treatment.

Target A1c is between 6.0 – 6.5% because he is young and newly diagnosed DM.
Should stress about lifestyle modification eg diet exercise and healthy eating, doing this should be able to bring down A1c level. Failing all the above then the third agent will be discussed.

**Slide 4**

**Case 2**

A 52-year-old man, diabetes and hypertension for 12 years with non proliferative retinopathy, nephropathy and had PCI to the right coronary artery recently.

BP: 143/87 mmHg, Weight: 92.1 kg, BMI: 27 kg/m²

Medications:
- SC Mixtard 30 units BD
- Metformin 500 mg BD
- Losartan 100 mg OD
- Bisoprolol 5 mg OD
- Aspirin 150 mg OD
- Plavix 75 mg OD
- Lipitor 20 mg ON

**Slide 5**

Investigation results:
- A1c: 8.5%
- FBS: 9.1 mmol/L
- Se creatinine: 125 umol/L
- E-GFR: 56 ml/min/1.73 m²
- TG: 2.11 mmol/L
- T-Chol: 5.12 mmol/L
- LDL-C: 2.74 mmol/L
- HDL-C: 1.1 mmol/L

**Slide 6**

Not monitoring blood glucose at home, therefore not adjusting blood glucose.
Had hypoglycaemic symptoms once in a while, but didn’t check the blood glucose level.

What is the recommended A1c level for this patient? What about his blood glucose level at home, is it important to monitor?
- The recommended A1c level for him is between 7.0 - 7.5% without the risk of hypoglycaemia
- It is important to monitor the blood glucose at home so the insulin dose can be adjusted accordingly.
- Also monitoring blood glucose at home would also help directly in achieving the A1c target.
**Case 3**

Mr B.A., a 37-year-old Indian man.
Polyuria and polydipsia of one week duration.
Recent weight loss.
F/H of diabetes: +

Weight 74 kg; BMI 28 kg/m²
Physical examination: NAD
Random blood glucose: 27 mmol/L

---

**Slide 8**

**Comment on this patient.**
- Has several risk factors:
  - Indian ethnicity
  - Family history of diabetes
  - Age over 30 years
  - Obese
- Symptomatic
- Hyperglycaemia

**How would you manage this patient?**
- Screen for other risk factors & diabetes related complications
- HbA1c will help decide on treatment regime

---

**Slide 9**

A1c was not done at diagnosis.
FBS 11.0 mmol/L.

Patient was started on:
- Gliclazide 40 mg bd
- Metformin 1gm BD

After 1 month:
- A1c 8.3%
- FBS 6.0 mmol/L
- 2hr PPG 7.0 mmol/L
Any comments on the A1c of 8.3%?
What would you do after this?

- A1c of 8.3% includes the period of hyperglycaemia at the time of diagnosis.
- A1c is an average of glucose over 3 months. Hence it can be predicted that the HbA1c will be less in the next few months.
- Furthermore there maybe some improvement in pancreatic function as glucose toxicity to beta cells is reduced.
- Hence it may not be necessary to add extra medications just yet.
Medical Nutrition Therapy & Low Glycaemic Index Diet
Medical Nutrition Therapy

- MNT is important in preventing and managing diabetes as well as delaying complications of DM.
- Proper diet is crucial at any stage of management of DM including those on medications.
- The goals of MNT together with medications are:
  - to attain, 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 co-morbidities such as hyperlipidaemia, hypertension and chronic kidney disease.

General recommendations

Diet counseling is effective to help lower A1c by an average of 1–2%.

Efficacy of Medical Nutrition Therapy

Evidence on Effectiveness of MNT

- Newly diagnosed type 2 diabetes
- 2%
- Type 2 diabetes with an average duration of 4 years
- 1%

Evidence from Diabetes Care 36, 1049-1053
- Herman et al. (1999) Diabetes Care 22, 1740-1747
- Herman et al. (2000) Diabetes Care 23, 1740-1747
Specific recommendations: Prevention of Diabetes

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.

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 kg per week. 3-4 months. 

Physical activity of 150 minutes per week or 30 minutes five days or more per week. 

Meat replacements (MRPs) can be used as part of a comprehensive meal plan for weight loss and weight maintenance. 

A combination of reduced calorie diet, physical activity and behaviour modifications can provide greater initial weight loss. 

Quick Guide of Selecting The Right MRP

<table>
<thead>
<tr>
<th>Calories</th>
<th>180 to 250</th>
</tr>
</thead>
<tbody>
<tr>
<td>For MRPs lower than 250 calories, add an extra 15 to 20 grams of carbohydrates (about 100 calories) by including fat-free light yogurt, low-fat whole-grain crackers, fresh fruit or fat-free milk. Raw or cooked non-starchy vegetables (which are low in calories but contribute extra fiber, vitamins and minerals) may be eaten with any of the MRPs.</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>10 to 15 grams</td>
</tr>
<tr>
<td>Adequate protein promotes health and mealtime fullestness.</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>14 to 34 grams</td>
</tr>
<tr>
<td>To slow the rate blood-glucose (sugar) rises after a meal, look for the first carbohydrate listed in the ingredients to be a multifiber or complex carbohydrate rather than refined sugars, such as sucrose, corn syrup, high-fructose corn syrup or brown rice syrup.</td>
<td></td>
</tr>
<tr>
<td>Dietary Fiber</td>
<td>3 to 6 grams</td>
</tr>
<tr>
<td>Total Fat</td>
<td>5 to 8 grams</td>
</tr>
<tr>
<td>The primary fat source should be unsaturated fat from vegetable oils rather than saturated fat, such as partially hydrogenated oil, palm oil or coconut oil. All MRPs should be trans-fat free.</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0 to 30 milligrams</td>
</tr>
<tr>
<td>Sodium</td>
<td>150 to 200 milligrams</td>
</tr>
<tr>
<td>Vitamins and Minerals</td>
<td>Look for 50 to 100 percent of the Dietary Reference Intake.</td>
</tr>
<tr>
<td>Avoid products containing stimulants, such as caffeine, spending, guarana and ginseng.</td>
<td></td>
</tr>
</tbody>
</table>

Specific recommendations: Prevention of Diabetes

A high dietary fiber diet is encouraged for the prevention of diabetes. A high fiber diet (20-30 g fiber/day) consisting of vegetables, fruits, legumes and whole grain cereals is encouraged. Higher consumption of whole grains can contribute to the prevention of T2DM. Higher consumption of whole grains should form 50% of the total grains intake as recommended by the Malaysian Dietary Guidelines, 2010.
Figure 2. Forest Plot Showing the Multivariate-Adjusted RR of Type 2 Diabetes for a Two-Serving-per-Day Increment in Whole Grain Intake for Individual Cohort Studies and All Studies Combined

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyer</td>
<td>0.85 (0.75-0.96)</td>
</tr>
<tr>
<td>Fung</td>
<td>0.80 (0.71-0.90)</td>
</tr>
<tr>
<td>Montonen</td>
<td>0.90 (0.81-1.01)</td>
</tr>
<tr>
<td>van Dam</td>
<td>0.65 (0.55-0.78)</td>
</tr>
<tr>
<td>NHSI</td>
<td>0.70 (0.62-0.79)</td>
</tr>
<tr>
<td>NHSII</td>
<td>0.83 (0.69-0.98)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.79 (0.72-0.87)</td>
</tr>
</tbody>
</table>

Relative risk: 4

SLIDE 8

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.

SLIDE 9

Specific recommendations: Dietary management

Total carbohydrate (CHO) intake should be monitored in patients with T2DM. There is no ideal percentage of energy for carbohydrate, protein, and fat for diabetes.

Carbohydrate restriction improves glycemic control, and reduces insulin fluctuations.

Glucose and insulin response for patients with type 2 diabetes on low-carbohydrate diet vs. control. Data indicates ~50% for 3 patients with type 2 diabetes after seven days on their usual high-carbohydrate diet (control) and after 2 weeks on a low-carbohydrate diet. Medication was reduced in 4 patients and discontinued in one during the low-carbohydrate diet.
SLIDE 10

The Best DIET?

CHO – 45-60% energy (min 130g)
Protein – 15-20% energy
FAT – 25-35% energy

SLIDE 11

Carbohydrate Intake – Malaysia

Figure 8: Changes in composition of calories from protein, fat and carbohydrates in Malaysia between 1961-2006
Source: plotted from data in FHO food balance sheet (1961-2006)

SLIDE 12

Rice, bread, cereals
Legumes & pulses
Fruits
Milk & milk products
Sugars, sweets, cakes, kuih

Whole grains should form 50% of the total grains intake as recommended by the Malaysian Dietary Guidelines 2010

ENCOURAGE WHOLEGRAINS, FRUITS, VEGETABLES, LEGUMES

MINIMIZE INTAKE OF SUGARY FOODS AND BEVERAGES

Foods with fewer than 20 calories and 5 grams of carbohydrate are considered “free.”
Based on 2-4 exchanges of CHO per meal. This is for 1600-1800 kcal a day.
**Slide 16**

What about snacks?

<table>
<thead>
<tr>
<th>Bread</th>
<th>Biscuits</th>
<th>Corn (6 inches)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popiah</td>
<td>Apam</td>
<td>Fruit</td>
</tr>
</tbody>
</table>

Snacks can be eaten in 1-2 servings as shown. Suitable for sedentary women & inactive men.

Snacks allowed for 1-2 exchanges. Can eat 1-2 times a day.

---

**Slide 17**

What about Fruits?

<table>
<thead>
<tr>
<th>Apple</th>
<th>Kiwi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaya</td>
<td>Orange</td>
</tr>
</tbody>
</table>

1 serving of fruit is as shown above. Fruits can be eaten 2-3 servings a day.

Based on 1 exchange of fruits.

---

**Slide 18**

**CONSISTENCY**

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.

It is prudent to individualise the distribution of the total CHO exchanges allowed in a day into meals according to the patient’s lifestyle.

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.
1 CHO exchange = 15g CHO, 65kcal

- Honey
- Jam
- Kaya
- Sugar
- Syrup
- Cocoa/ Malt-based Powder
- Condensed Milk
- Candy

= 1 teaspoon = 5g
= 1 tablespoon = 10 g

Sucrose (e.g. table sugar) intake must be counted as part of the total carbohydrate intake. (Level III)

Excess sucrose intake contributes to calories and may cause weight gain. (Level III)

The top 10 natural sources of aspartame

The European Food Safety Authority (EFSA) conducted a comprehensive review of the evidence in 2013 and concluded that aspartame was safe for human consumption, including pregnant women and children.

Acceptable Daily Intake: 40-50mg per kg of body weight. (set at 100X safety factor based on animal toxicology studies)

Non-nutritive sweeteners do not impact glycaemic level. (Level II)
Intake should not exceed Acceptable Daily Intake (ADI) levels.

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

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. (Level II)
Controlling blood cholesterol

- Weight reduction
- Saturated fat and cholesterol
- Reduce trans fatty acids intake
- Physical activity
- Increase fiber intake

Controlling blood pressure

- Weight reduction
- Dietary sodium reduction
- Limit alcohol use
- Physical activity
- Fruits and vegetables

Cardiovascular Health Diet

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

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

Effects of Reducing PPHG

![Graph showing risk of progression to diabetes, cardiovascular events, and development of new cases of hypertension.]

---

**SLIDE 26**

**Patients With Type 2 Diabetes May Spend More Than 12 Hours per Day in the Postprandial State**

- Postprandial
- Postabsorptive
- Fasting

![Bar graph showing duration of postprandial state at different times of day (breakfast, lunch, dinner, midnight, 4 AM, breakfast).]


---

**SLIDE 27**

**Non-pharmacological treatment for PPG**

- Weight Loss
- Exercise
- Glycemic effect of meals
  - Portion Size – esp CARBOHYDRATES
  - Glycemic Index (GI) & Glycemic Load (GL)
**Definition of Glycemic Index**

As defined, the GI takes into account only the type of carbohydrate in food and ignores the total amount of carbohydrate in a typical food serving, both the type and amount of carbohydrate influence the postprandial and insulin responses of a given ingested food.

Ref: F Xavier Pi-Sunyer, AJCN 2002

---

**Benefits of Low GI Diet**

Low GI diet helps lower blood glucose levels. Meta-analysis of 14 studies, 356 subjects (types 1 & 2 DM), 2-52 weeks duration

- Low GI foods...
  1. Reduces postprandial blood glucose
  2. Reduce CRP-Protein
  3. Lowers HBA1c: by 0.14% to 0.5%

Mean difference

- 0.4% points in HBA1c over & above reduction from high GI diet

---

**Factors Influencing GI Ranking**

- Type of starch
- Cooking
- Physical entrapment
- Food processing
- Viscosity of fiber
- Acid content
- Sugar content
- Fat content
- Protein content

---
Slide 31

![Glycemic Index of Foods Table]

When substituting high GI foods with low GI choices, the principles of a healthful diet must still be adhered.

Slide 32

**Tips to incorporate GI into meals**

- Choose less refined and unprocessed foods
- Consume at least 1 low GI food at each meal
- Add high fiber and soluble fiber foods e.g. legumes
- Add lean proteins & healthy oils in meals: can help lower GI of meals
- Do not overcook starches and grains
- Monitor portion size
- Eat less ripe fruits e.g. less ripe bananas
- Food combination: mix high GI with low GI foods in meals

Slide 33

**Summary**

- Medical nutritional therapy is the mainstay of prevention and treatment of T2DM. [Grade A]
- 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]
- 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]
- Monitoring carbohydrate intake is important in management of T2DM. [Grade A]
- Substituting low GI foods for higher GI foods at mealtime reduces postprandial blood glucose. [Grade A]
Case Study

medical nutrition therapy & low glycaemic index diet
Slide 1

**Case**

Mr LG is a 45-year-old Indian who works as marketing manager, married with 2 young kids, wife is a teacher and his work is stressful.

Family history of diabetes: father & 1 older sibling

6 months ago, diagnosed with T2DM.

---

Slide 2

**Past Medical History**

Past episodes of nocturia, advised to lose weight 10 kg but no further action taken.

Medications:
- Metformin 500 mg BD
- Atorvastatin 10 mg daily
- Irbesartan 150mg OD

---

Slide 3

**Physical Examination**

Heart normal, lungs clear
Examinations of the thyroid and abdomen normal
Fundi – clear, no retinopathy.
Neurological test – ankle reflex +ve,
Foot exam - normal sensation to light touch and no skin or toenail lesions.
Physical Examination

- Weight: 80 kg; Height: 1.65 m; BMI: 29.4 kg/m²
- Waist circumference: 110 cm
- Blood pressure: 140/90 mmHg (sitting); Pulse 70 beats/min
- Respiratory rate: 20 breaths/min
- Temperature: normal

Blood results

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
</tr>
</thead>
</table>
| Glucose     | Fasting: 7.0 mmol/L  
              | Post meals: 9.2 mmol/L |
| A1c         | 6.9%             |
| T-Cholesterol| 5.8 mmol/L      |
| HDL-C       | 1.1 mmol/L       |
| TG          | 4.2 mmol/L       |
| LDL-C       | 2.7 mmol/L       |
| Urine microalbumin | Nil           |
| Renal profile| Normal values   |

Patient’s perception of his diabetes management

- “I never eat anything sweet! My father and brother are diabetics, so I know. My wife always buys these herbal remedies and some weight-loss powders, and she frequently scans the Internet for the latest diabetes remedies…but all these don’t seem to help”.
- Limited exercise & high carbohydrate intake
- No SMBG - “What would knowing the numbers do for me? The doctor already knows the sugars are high.”
- Poor understanding of diabetes
- Does not want to add any other medication He stated that one new medication at a time was enough and that “too many medications would make a sick man out of me.”
**Slide 7**

*Food/nutrition history*

- Patient has smoked for over 15 years (quit 1 year ago) and drinks alcohol 1-2 times per week.
- Trying to lose weight and increase his exercise for the past 1 year without success.
- Highest weight was 85 kg about 2 years ago. Lowest was 70 kg when he was around 35 years old and before the kids arrived, and he was a member of a badminton club.
- Lately job stressful, comes home late and difficult to find time to exercise. Complains that it has been raining a lot lately in the evenings.

**Slide 8**

*Usual Intake*

1. **Breakfast (10 am)**
   - Teh Tarik less sweet 1 glass
   - Date 6" 2 pieces @ white/wholemeal bread 2-3 pieces @ iodized salt 2 pcs

2. **Lunch/Dinner (1.30 pm/ 8pm)**
   - Parboiled rice 3-4 scoops
   - Stir-fried green vegetables 1 scoop
   - Fish/chicken 1 portion (1 palm size) – curry/fried
   - Lunch usually larger than dinner

3. **Afternoon tea (4 pm)**
   - Tea ‘O’ with no sugar
   - Cream crackers 3-4 pieces

*Food Checklist*
- Sweet Indian kuih once a while, a little bit
- Beer – 1 can – drinks with friends 1-2X/week
- SMOKING – 1 packet/day

**Slide 9**

*Question 1*

What would be your conclusions from Mr LG’s assessment?

- Obesity
- Hyperlpidemia
- Hypertension
- Self management/lifestyle deficits
- Postprandial hyperglycemia
- Cardiovascular risk
- Retinopathy
- Nephropathy
- Peripheral Neuropathy
- Sedentary lifestyle
- Poor dietary habits
- Elevated urine microalbumin level
- Metabolic Syndrome
Question 2
What would be the priority management for Mr LG?

- Smoking cessation
- Reduce carbohydrate intake
- Low glycemic index diet
- Intensive lifestyle / behaviour modification
- All of the above

Question 3
What can be recommended to Mr LG to lose weight?

- Exercise
- Reduce carbohydrate intake
- High protein diet
- Reduce portion size
- Eat a low fat diet to reduce calories
- Use meal replacements – energy bars, liquid shakes

Question 4
What dietary practices by Mr LG would be of concern?

- Too many meals
- Too much sugary foods
- Lack of wholegrain carbohydrate choices
- Low fruits and vegetables intake
- Carbohydrate portions too large
- High glycemic index food choices
- Alcohol intake
TRAINING MANUAL FOR HEALTHCARE PROFESSIONALS
MANAGEMENT OF TYPE 2 DIABETES MELLITUS
(5th Edition)

SLIDE 13

Usual Intake

1. Breakfast (10 am)
   - Teh Tarik w/ sweet 1 glass
   - Ouse 6“ 2 pieces @ white/wholemeal bread 2-3 pieces @ idli/capati 2 pcs

2. Lunch/Dinner (1.30 pm/ 8pm)
   - White parboiled rice 3-4 scoops
   - Stir-fried green vegetables 1 scoop
   - Fish/chicken 1 portion (1 palm size) curried
   - Lunch usually larger than dinner

3. Afternoon tea (4 pm)
   - Tea “O” with no sugar
   - Cream crackers 3-4 pieces

Food Checklist
- Sweet Indian kuihs once a week, a little bit
- Beer – 1 can – drinks with friends - 1-2X/week

SLIDE 14

Question 5
What dietary measures would you recommend to lower his HBA1c?

- Reduce weight
- Reduce carbohydrate intake
- Increase protein intake
- Increase fruits and vegetables intake
- Exercise
- Low Glycemic Index food choices

SLIDE 15

Question 6
What changes should Mr LG do to his diet?

- Use meal replacements
- Skip dinner and substitute with oats
- Avoid rice, dosai, idli and capati
- Follow Atkins diet
- Follow Healthy Plate portions: half vege, quarter fish, quarter brown rice/parboiled rice
- Add low GI fruits after meals during lunch and dinner
- Add beans / lentils during meals
- Mix brown rice or oats in rice
- Avoid Teh Tarik completely and switch to Chinese tea only
- Use olive oil for cooking
- Stop eating out
- Stop alcohol
Question 7
Mr LG wishes to take special products (energy bars/liquid shakes/protein powders) for controlling his blood sugar. Do you agree?
- YES
- NO

Question 8
What other lifestyle changes can he make?
- Increase physical activity or exercise

Physical Activity
- Make time for exercise: late evenings/after work, weekends.
- Brisk walking 20 minutes most days of the week, gradually build up to 30-45 minutes.
- Increase daily activities: use stairs, wash car, help in housework, wear pedometer to monitor increasing steps taken/day (aim 10,000 steps/day).
TOPIC 5

physical activity
SLIDE 1

**Response to 100 g of glucose in mild Type 2 Diabetics**

12 months of Training

![Graph showing plasma glucose and insulin levels before and after training](image)


SLIDE 1

**Response to 100 g of glucose in mild Type 2 Diabetics**

12 months of Training

![Graph showing plasma glucose and insulin levels before and after training](image)


SLIDE 3

**Benefits of physical activity**

Better blood glucose control
1. Improved insulin sensitivity
2. Blood glucose lowering effect

Exercise alone - decrease of 0.66% in HbA1c
- (ex.) 8-9% improvement to ideal level of <7.0%

Diet + Exercise - decrease of 0.76% in HbA1c
- (ex.) 9-10% improvement to ideal level of <7.0%

Hypoglycemia during or after Exercise

It will most likely occur if the patient:
- Takes insulin or diabetes pill.
- Skips a meal.
- Exercises for a long time.
- Exercises strenuously.

If it occurs, what can be done?
- Patient must eat a snack before exercise, or
- Adjusts the medication dose.
- Remember:
  - Patient should always carry a source of CHO with him (An apple or orange juice, or a piece of fruit).

Snacking to prevent hypoglycemia

Basic Rules:
1. Snack prior to activity to prevent hypoglycemia
2. Adjust quantity based on pre-activity BG or direction of BG
   - BG low or dropping: < usual carbs
   - BG OK or stable: usual carbs
   - BG High or rising: > usual carbs
3. Snack at least once per hour during prolonged activity
4. Choose high-glycemic forms of carbohydrate

Source: Scheiner, Gary. Think Like A Pancreas, Marlowe Publishing, NY, 2005

Which approach keeps BG in range for the majority of the workout?

Source: Scheiner, Gary, MS CDE
Recommendation 1

1. Patients with should exercise 5 days a week, preferably most days of the week and with no more than 2 consecutive days without physical activity.

Recommendation 2

2. 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.

Recommendations 3 and 4

3. 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.

4. Overweight and obese individuals should gradually increase physical activity to 60–90 minutes per day for long term weight loss.
Recommendation 5

5. Patients with diabetes with possible cardiovascular disease who wish to undertake exercise that is substantially more vigorous than brisk walking, should have medical evaluation for conditions that might increase exercise-associated risk.

6. The evaluation would include history, physical examination (including fundoscopic exam, foot exam, and neuropathy screening), resting ECG, and, possibly, exercise ECG stress testing.
Case Study

physical activity
Case

A 52-year-old Malay lady, working as a chief clerk in JPA, Putrajaya.

She has been diagnosed with Type 2 DM for the past 7 years and hypertension for the past 4 years.

Her elder brother is also diabetic and recently had an ischaemic stroke.

Case

Physical activity

• Only walks from parking lot to her office, took about 5 minutes everyday. She avoid using stairs, does not want to break a sweat at work.

• During weekends, she will be doing all the housework, cooking and cleaning since both her children have gone to college.

Current medications:

• Metformin 1 g bd
• Acarbose 100 mg tds
• Perindopril 8 mg od

Case

Clinical examination:

Height: 1.62 m, Weight: 88.1 kg, BMI: 33.6 kg/m²

Waist circumference: 101 cm

BP: 132/78 mmHg, PR: 80 beats/minute

Acanthosis nigricans at back of the neck

CVS/Lungs: within normal

She has no peripheral neuropathy.
Comment on her BMI?
- BMI range: obese class 1.
- Sedentary lifestyle

What are her risk factors?
- Age over 30 years
- BMI = 33.6 kg/m² - obese
- WC >80 cm (for women) – central obesity
- Sedentary lifestyle
- Combination of several NCD risk factors - She is at high risk.

Lab Results:
- FPG : 9.2 mmol/L
- A1c : 7.0 %
- Total cholesterol : 5.4 mmol/L
- LDL-C : 2.9 mmol/L
- HDL-C : 0.8 mmol/L
- Triglycerides : 1.9 mmol/L
- Creatinine : 70 μmol/L
- No proteinuria

Comment on her lab results.
- Elevated fasting glucose, A1c, total cholesterol, LDL cholesterol and triglycerides
- Low HDL cholesterol.
- His creatinine levels are in the normal range.
Progress

Patient’s main concern is her weight gain.
She says she has no time to exercise
• Our main concerns are:
  • Obesity and the need for lifestyle modifications.
  • Glycaemic control not to target
  • Raised T Cholesterol, LDL, TG and low HDL.

What need to be done with regards to her lifestyle?

1. Refer to dietitian for low calorie diet.
2. Increase physical activity.

Any preliminary test to do prior to starting exercise?

Pre Exercise Assessment:
• Assess target organ complications: Peripheral neuropathy, retinopathy, nephropathy and CVD risk assessment.
• Assess knowledge on diabetes, particularly on patient’s knowledge on benefit of exercise and how to initiate exercise program. Risk of hypoglycaemia if on insulin or SUs
• Assess readiness for exercise.
• Assess blood glucose before exercise.

What would you suggest her to do?

To increase physical activity at work:
• Increase the unplanned exercise at her office and reduce sedentary time.

Example:
• Increase walking, gardening, mop the floor
• Begin regular aerobic exercise.
• Begin regular resistance exercise.
Exercises at work place

- Park the car farther away from the office. Walk an extra mile.
- Take the stairs, avoid using the elevators.
- Walk while talking on the phone.
- Walk the hallway, do your own errands.
- Calf raises. Stand in front of a desk, raise your heels of the floor and slowly lower them.
- Leg extensions. While sitting in your chair, extend your right leg until it is level with your hip. Hold for 30 seconds and alternate sides.

Exercises at work place

- Hip flexions. While sitting in your chair, lift your right foot a few inches off of the floor. Keep your knee bent at a 90 degree angle and hold the position as long as you are comfortable.

- Water bottle weights. Use a full water bottle as weight. You can do front raises, overhead presses and bicep curls with a water bottle.

Small changes make a “weight” difference

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>Yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduced Intake/Expenditure (kcal)</td>
<td>Total Intake/Expenditure (kcal)</td>
</tr>
<tr>
<td>Slow walk for 30 mins/day</td>
<td>89</td>
<td>32,485</td>
</tr>
<tr>
<td>Brisk walk for 30 mins/day</td>
<td>130</td>
<td>47,085</td>
</tr>
<tr>
<td>Jog for 30 min/day</td>
<td>252</td>
<td>91,980</td>
</tr>
<tr>
<td>Reduce intake of 2 tsps sugar/day</td>
<td>40</td>
<td>14,600</td>
</tr>
<tr>
<td>Reduce intake of 2 tsps oil/day</td>
<td>90</td>
<td>32,850</td>
</tr>
<tr>
<td>Switch to drink lemon tea (no sugar) instead of milk tea</td>
<td>113</td>
<td>41,245</td>
</tr>
<tr>
<td>Drink 1 can less of soft drink/day</td>
<td>150</td>
<td>54,750</td>
</tr>
</tbody>
</table>

Courtesy from Dr Ronald Ma CW, H. Kong
oral anti-diabetic medications
Oral Anti-Diabetic (OAD) Agents

There are currently 6 classes of OAD agents:

1. Biguanides
2. Insulin Secretagogues
   - Sulphonylureas
   - Meglitinides
3. Alpha-glucosidase inhibitor (AGIs)
4. Thiazolidinediones (TZDs)
5. Dipeptidyl peptidase-4 (DPP-4) inhibitors
6. Na-Glucose Co-Transporter 2 (SGLT2) inhibitors

Slide 2
Biguanides (Metformin)

- Metformin lowers blood glucose especially fasting blood glucose by decreasing hepatic glucose production
- Usage in combination with other OAD agents have synergistic effect to further reduce blood glucose and may reduce insulin requirements.
- Most common adverse effects are nausea, anorexia and diarrhoea.
- Minimised if metformin
  - taken together with or after meals.
  - best to start with a single daily dose, followed by weekly titration
  - Extended release formulation also reduces side effects

Slide 3
Biguanides (Metformin)

- One of the complications of long term metformin therapy is vitamin B12 deficiency.
- Lactic acidosis is rare and usually associated with renal impairment
- One of the benefits of metformin is weight stability or mild weight loss.
- Dose beyond 2000 mg OD does not confer any further glycaemic benefit and significantly increase gastrointestinal side effects.
Biguanides (Metformin)

- Low dose metformin can be safely prescribed to lactating mothers
- The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes
- Avoid if creatinine >150 umol/l or creatinine clearance <30 mL/min

Metformin Formulations and Dosage

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

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

Insulin Secretagogues (SUs)

- SUs lower plasma glucose by increasing insulin secretion
- Major adverse side effect is hypoglycaemia. Risk higher in renal impairment, liver cirrhosis and elderly
- Weight gain is common
- Second generation SUs (Glimepiride, Gliclazide MR) cause less risk of hypoglycaemia and less weight gain
**Insulin Secretagogues (SUs) (cont.)**

- 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.
- SUs can be combined with other OAD agents or insulin to improve glucose control, if indicated.
- SUs should be taken 30 minutes before meals, except Glimepiride and Gliclazide MR which can be taken just before the meal.

**SU Formulations and Dosage**

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

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

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

**Meglitinides**

- Short acting insulin secretagogues which stimulate insulin secretion, although they bind to a different site within the SU receptor.
- Shorter circulating half life than SUs, rapidly absorbed from the GI tract with peak level 1-hour post administration and eliminated within 4-6 hours.
- It should be taken within 10 minutes before main meals.
- Can be added to other OAD(s) except SU.
Meiglitinides (cont.)

- Associated with less risk of weight gain compared to SUs and hypoglycaemia may be less frequent
- Primarily use to control PPG

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

Alpha-glicosidase inhibitor (AGIs)

- AGIs e.g. acarbose reduces the rate of digestion of polysaccharides in the proximal small intestine by inhibiting α-glucosidase enzymes. They should be taken with main meals
- Lowers postprandial glucose without causing hypoglycaemia
- Less effective in lowering glycaemia than metformin or SU
- Synergistic effects when used with other OAD agents and may be combined with insulin

Alpha-glicosidase inhibitor (AGIs) (cont.)

- If hypoglycaemia occurs when used in combination with SUs or insulin, advise patients to take monosaccharides, e.g. glucose
- Commonest side effects are bloating, abdominal discomfort, diarrhoea and flatulence

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose 50 mg / 100 mg tablet</td>
<td>Initial dose 50 mg OD</td>
<td>100 mg TDS</td>
</tr>
</tbody>
</table>
Thiazolidinediones (TZDs)

- Peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists and act primarily by increasing insulin sensitivity in muscle, adipose tissue and liver
- Improvement in glycaemic control may only be seen after 6 weeks and maximal effect at 6 months
- Side effects include weight gain (due to redistribution of body fat), heart failure, macular edema and osteoporosis

Thiazolidinediones (TZDs) (cont.)

- Contraindicated in patients with CCF and liver failure
- Use of TZDs as first line therapy has been found to have greater durability in glycaemic control compared to metformin and SU
- Use of TZDs with insulin is not recommended.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone 4 / 8 mg tablet</td>
<td>4 mg OD</td>
<td>8 mg OD</td>
</tr>
<tr>
<td>Pioglitazone 15 / 30 mg tablet</td>
<td>15 mg OD</td>
<td>45 mg OD</td>
</tr>
</tbody>
</table>
DPP-4 Inhibitor

- Minimal risk of hypoglycaemia and weight neutral
- Efficacy not influenced by the duration of T2DM
- SAVOR-TIMI 53 trial has shown that use of saxagliptin associated with increased risk for hospital admission for heart failure
- TECOS study did not show any increased risk of hospitalisation for heart failure with sitagliptin
- In general, the use of DPP-4 inhibitors not associated with any adverse cardiovascular outcomes

DPP-4 Inhibitors Formulations and Dosage

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

*For fixed combination formulations, please refer to specific product inserts

DPP-4 Inhibitors: A Pharmacokinetic Comparison

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>mg</th>
<th>t_{1/2} (hr)</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>qd</td>
<td>100</td>
<td>~12</td>
<td>Unchanged</td>
<td>&gt;80% urine</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>bid</td>
<td>50</td>
<td>~3</td>
<td>Inactive metabolites</td>
<td>*85% urine</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>qd</td>
<td>5</td>
<td>~3</td>
<td>Active metabolite</td>
<td>&gt;60% urine</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>bid</td>
<td>5</td>
<td>&gt;10</td>
<td>Mostly unchanged</td>
<td>*80% bile</td>
</tr>
</tbody>
</table>
SLIDE 22

**SGLT2 inhibitor: A novel insulin-independent approach to remove excess glucose**

SGLT2 inhibitors selectively inhibit SGLT2 in the renal proximal tubule.

SLIDE 23

**Normal glucose homeostasis**

Net balance ~0 g/day

- Glucose input ~250 g/day:
  - Dietary intake ~180 g/day
  - Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

- The kidney filters circulating glucose

- Glucose filtered ~180 g/day

- Glucose reabsorbed ~180 g/day

SLIDE 24

**Glucose handling in Type 2 diabetes**

- Glucose input >200 g/day:
  - Dietary intake >180 g/day
  - Glucose production >100 g/day
  - Gluconeogenesis
  - Glycogenolysis

- Average blood glucose concentration 130 mg/dL
- Kidney filters all circulating glucose
- Glucose filtered ~270 g/day

- Increased reabsorption and recirculation of glucose
- Above the renal threshold for glucose (180 mg/dL), glucose is excreted in the urine (glucosuria)
**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**

- Inhibits SGLT2, a transporter in the proximal tubule, reducing glucose reabsorption leading to an increase in urinary glucose excretion.
- Accompanied by weight loss and modest blood pressure reduction together with lower risk of hypoglycaemia.
- Not recommended for those on concomitant treatment with loop diuretic.
- Efficacy dependent on renal function and not recommended in patients with renal impairment (e-GFR <60 L/min/1.73 m²).

---

**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**

- Can be combined with other OAD(s) to improve glucose control.
- 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.
- US FDA has issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture.

---

**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors**

- Few cases of euglycaemic diabetic ketoacidosis (DKA) had been reported in patients on SGLT2 inhibitors and caution should be exercised when prescribing in those with severe beta-cell insufficiency, latent autoimmune diabetes and in post-surgical patients.
- EMPA-REG clinical trial conducted inT2DM patients with prior cardiovascular events showed a lower rate of cardiovascular events and all-cause mortality. The reasons behind these findings yet to be determined.
**SLIDE 28**

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

**SLIDE 29**

General Guidelines for Use of OAD Agents

- OAD can be used as monotherapy or in combination with other OAD(s), and/or injectable agents (e.g., insulin, GLP-1 receptor agonist).
- Agents that are known to improve fasting hyperglycaemia include metformin and TZDs while others reduce mainly postprandial hyperglycaemia.
- As first line therapy, metformin is the preferred choice. Other OAD agents are acceptable alternatives.
- If glycaemic targets are not achieved, intensification of treatment should be made every 3 months.
- If monotherapy fails, combination of other agents is recommended.

**SLIDE 30**

What Comes After Metformin? Depends …

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Drug characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of hyperglycemia</td>
<td>BG lowering efficacy &amp; durability</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Risk of inducing hypoglycemia</td>
</tr>
<tr>
<td>Weight</td>
<td>Effect on weight</td>
</tr>
<tr>
<td>Comorbidities (renal, cardiac, hepatic)</td>
<td>Contraindications &amp; side effects</td>
</tr>
<tr>
<td>Access to treatment</td>
<td>Cost and coverage</td>
</tr>
<tr>
<td>Patient preferences</td>
<td>Other</td>
</tr>
</tbody>
</table>

Metformin is first line agent in most patients: if not using metformin, think of **why not**. Safe, effective in lowering BG and benefit in obese CV patients. Other considerations in choosing agent are renal function and weight neutrality.
General Guidelines for Use of OAD Agents

- 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.
- OAD agents are not recommended for diabetes in pregnancy.

Treat multiple pathophysiological abnormalities that contribute to hyperglycaemia in T2DM

...before initiating insulin as long as A1c < 10%

**SLIDE 34**

**Multiple, Complex Pathophysiological Abnormalities in T2DM**

- **GLP-1R agonists**
- **Insulin**
- **Amylin mimetics**
- **Glinides**
- **DPP-4 inhibitors**

**HYPERGLYCEMIA**

- **T2D**

Adapted from: Inocchi SE, Shennan HJ, in: Cecil Medicine, 2011.

**SLIDE 35**

### Table 21: Treatment Recommendations for Patients on Clinico Follow-up

<table>
<thead>
<tr>
<th>Glycemic Control</th>
<th>A1c &lt; 6.5% or FPG &lt; 90 mg/dL</th>
<th>A1c 6.5—7.5% or FPG 90—105 mg/dL</th>
<th>A1c 7.5—9.0% or FPG 105—150 mg/dL</th>
<th>A1c &gt; 9.0% or FPG &gt; 150 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Start metformin (or metformin not tolerated, use an agent from Box 1)</td>
<td>Start metformin and another agent from Box 1 (dual therapy)</td>
<td>Start metformin and another agent from Box 1 (dual therapy)</td>
<td>Start metformin &amp; another agent + exenatide basal or premixed insulin</td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td>Use metformin (preferred)</td>
<td>Add 2 agents from Box 1 (dual therapy)</td>
<td>Add 2 agents from Box 1 (dual therapy)</td>
<td>Initiate insulin (short or premixed)</td>
</tr>
<tr>
<td><strong>Dual Therapy</strong></td>
<td>Add 1 agent from Box 1 (monotherapy)</td>
<td>Add 1 agent from Box 1 (monotherapy)</td>
<td>Add 1 agent from Box 1 (monotherapy)</td>
<td>Initiate insulin (short or premixed)</td>
</tr>
<tr>
<td><strong>Triple Therapy</strong></td>
<td>Add 2 agents from Box 1 (monotherapy)</td>
<td>Add 1 agent from Box 1 (monotherapy)</td>
<td>Add 1 agent from Box 1 (monotherapy)</td>
<td>Initiate insulin (short or premixed)</td>
</tr>
</tbody>
</table>

*MO = Multiple daily injections. *i*; *Intensify involves changing the regimen: SU = sulfonylureas*

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

- **Metformin**
  - **Effects:** Efficacious, risk of hypoglycemia, weight gain
  - **Effects:** Efficacious, risk of hypoglycemia, weight gain
  - **Effects:** Moderate efficacy, low risk of hypoglycemia, weight neutral
  - **Effects:** Moderate efficacy, low risk of hypoglycemia, weight neutral

- **Sulfonylureas**
  - **Effects:** Moderate efficacy, low risk of hypoglycemia, weight neutral
  - **Effects:** Moderate efficacy, low risk of hypoglycemia, weight neutral

**SLIDE 36**

### Suggested Treatment Approach for Specific Patient Profiles

- **Normal Weight**
- **Overweight**
- **Obese**
- **Increased Risk of Hypoglycemia**

**CKD Stage 3-5**

- **Consider first line:** metformin
- **Consider second line:** GLP-1 receptor agonist
- **Consider third line:** SGLT2 inhibitor
- **Consider fourth line:** basal insulin

**Notes:**
- 1st GLP-1 RA selected 2nd generation sulfonylurea/glinide DPP-4 inhibitor pioglitazone 4th line. SGLT2: sodium-glucose co-transporter 2 inhibitor.
- Avoid use of glitazone in patients with CKD. DPP-4 inhibitors should be started over GLP-1 RA in candidates.

- Patients with severe cardiovascular and/or existing diabetes should be discussed with the treatment team.
- Renal function may be considered in patients with BMI > 30 kg/m² and diabetes not controlled by lifestyle changes and pharmacotherapy.
**SLIDE 37**

**Weight gain in T2DM: a common side effect post treatment**

The vicious circle of type 2 diabetes

- **Obesity**
- **Insulin resistance**
- **Type 2 diabetes**

**Weight gain is a common side effect of diabetes treatments**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>-3.3</td>
</tr>
<tr>
<td>Sitagliptin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.4</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.9</td>
</tr>
<tr>
<td>Weight loss&lt;sup&gt;5&lt;/sup&gt;</td>
<td>3.3</td>
</tr>
<tr>
<td>Metformin + SU&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.3</td>
</tr>
<tr>
<td>Metformin + TZD&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**SLIDE 38**

**Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment**

- **Acceptable to use**
- **Do not use**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (ml/min)</th>
<th>Acceptable to use</th>
<th>Do not use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin&lt;sup&gt;4,8,9&lt;/sup&gt;</td>
<td>Unchanged</td>
<td>&gt; 60</td>
<td>60-30</td>
<td>&lt; 30</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

- **Metformin is eliminated renally, and (rare) cases of lactic acidosis have been described in CKD patients<sup>10</sup>**
- **In T2DM patients<sup>11</sup>:**
  - Reduce dose if GFR < 45 ml/min
  - Do not use if GFR < 30 ml/min

*Note: Dose adjustment required*

**SLIDE 39**

**Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)**

- **Acceptable to use**
- **Use with caution**
- **Do not use**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolites</th>
<th>Route of Elimination</th>
<th>eGFR (ml/min)</th>
<th>Acceptable to use</th>
<th>Use with caution</th>
<th>Do not use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimperide</td>
<td>Active</td>
<td>&gt; 60</td>
<td>60-30</td>
<td>&lt; 30</td>
<td>&lt; 15</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Inactive</td>
<td>&gt; 60</td>
<td>60-30</td>
<td>&lt; 30</td>
<td>&lt; 15</td>
<td></td>
</tr>
<tr>
<td>Glitazide</td>
<td>Inactive</td>
<td>&gt; 60</td>
<td>60-30</td>
<td>&lt; 30</td>
<td>&lt; 15</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Dose adjustment required*
**SLIDE 40**

### Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)

- **Repaglinide**  
  - Metabolites: Inactive  
  - Route of Elimination: ~ 90% bile  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ✓, < 30 - ✓, < 15 - X

- **Pioglitazone**  
  - Metabolites: Active  
  - Route of Elimination: ~ 55% bile  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ✓, < 30 - ✓, < 15 - X

- **Acarbose**  
  - Metabolites: formed in gut  
  - Route of Elimination: ~ 2% urine  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ✓, < 30 - X, < 15 - X

*Note: Dose adjustment required.*

**SLIDE 41**

### Use of Glucose-Lowering Agents in T2DM Patients with Renal Impairment (cont)

- **Exenatide**  
  - Metabolites: Mostly eliminated through glomerular filtration  
  - Route of Elimination: Mostly urine  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ? (use with caution), < 30 - X, < 15 - X

- **Liraglutide**  
  - Metabolites: Degraded in the circulation, liver, and kidney  
  - Route of Elimination: Partly urine  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ?, < 30 - X, < 15 - X

- **Insulin**  
  - Metabolites: Degraded in the circulation, liver, and kidney  
  - Route of Elimination: Partly urine  
  - eGFR (mL/min): > 60 - ✓, 60-30 - ✓, < 30 - ***, < 15 - ****

*Note: Dose adjustment required.*

**SLIDE 42**

### Efficacy of Various Anti-diabetic Agents

**Table**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sulfonylurea</th>
<th>GLAX</th>
<th>AS1</th>
<th>T2D</th>
<th>DPP4-inhibitors</th>
<th>SGLT2-inhibitors</th>
<th>GLP-1R agonists</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction, %</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
<td>4-8</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
<td>-1-1</td>
</tr>
<tr>
<td>Gastrointestinal adverse effects</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Cardiovascular disease (events per 1000 person-years)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bone loss</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
</tr>
<tr>
<td>CHD</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
<td>1-2%</td>
</tr>
</tbody>
</table>

**Notes:**
- **MET**: metformin; **SU**: sulfonylurea; **GLAX**: glimepiride; **AS1**: glimepiride-like agent; **T2D**: thiazolidinedione; **DPP4**: dipeptidyl peptidase-4 inhibitor; **SGLT2**: sodium-glucose cotransporter 2 inhibitor; **GLP-1R**: glucagon-like peptide 1 receptor agonist.
- The efficacy data for the above anti-diabetic agents were established with baseline A1C level below 10%. Efficacy of all DAs 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**
Slide 43

Proactive management of glycaemia: Early combination approach

- Diet
- OAD monotherapy
- OAD combinations
- OADs up-titration
- OAD + basal insulin
- OAD + multiple daily insulin injections

Slide 44

Treatment strategy

- Choice of monotherapy — cost, availability, durability of drug, fit the phenotype
- More aggressive strategy — combination therapy for those with more severe hyperglycemia at diagnosis
- Earlier intensification of treatment
- Rational use of drugs with complementary mechanisms of action
- Ongoing patient education — adherence to lifestyle interventions and pharmacotherapy

Slide 45

“The ability of clinicians to judge the merits of new medications is already limited — most receive their information about them from drug companies’ representatives and promotional materials.”

Summary

- Need to treat early & more aggressively.
- Treat to goal, treat to phenotype, individualised.
- Early combination therapy but keep regimens simple.
- Achieve effective and sustained glycaemic control.
- Continuous strong multidisciplinary patient support and education.
Case Study

oral anti-diabetic medications
**Case 1**

Madam J.A., a 58-year-old lady, housewife  
Duration of diabetes < 1 year  
History of hysterectomy  
F/H nil

On examination:  
Weight 110 kg; BMI 47 kg/m²  
Acanthosis nigricans noted  
BP 140/79 mmHg

Current treatment:  
- Metformin 1 gm TDS  
- Perindopril 4 mg od  
- Indapamide 1.5 mg od

**Investigation results:**  
- A1c 9.2%  
- FBS 10.9 mmol/L

**Comment on her status?**  
- Severely obese  
- Poor glycaemic control  
- High BP  
- Weight management is essential as insulin use may result in further weight gain  
- Refer obesity clinic

**How would you manage this patient?**  
- Add GLP1-RA or SGLT2i  
- Look for obesity related complications:  
  - OSA, OA, heart failure
Follow up 3 months later…

She was put on SGLT2i 3 month ago
Still on Metformin 1 gm TDS
A1c 7.6%; FBS 7.2 mmol/L
Weight lost 4 kg
BP 106/55 mmHg

Case 2

Mr. D.K., a 50-year-old Indian man
Weight 64.5 kg; BMI 22.5 kg/m²
Has family history of diabetes
Duration of diabetes: 5 years
A1c 8.6%
Current medications:
   Metformin 250 mg TDS
   Gliclazide 80 mg BD

What are your comments on the management of this patient initially?
- Poor glycaemic control, not reaching target
- Increase dose of OADs
On Follow-up...

At the last follow-up, the OADs doses were increased:
- Metformin 1 gm BD
- Gliclazide 120 mg BD
Weight 68 kg
A1c 6.7%

Subsequent Follow-ups...

A1c remained < 7.0%
Noted elevated post prandial blood glucose of 10-11 mmol/L

Do you want to do anything else?
If yes, what would you do?
- May start acarbose/glinide/DPP4-i/SGLT2i to address the post prandial hyperglycaemia

Case 3

Madam F.H, a 51-year-old Malay lady, housewife
T2DM 3 years, no complications
Currently on:
- Glibenclamide 10 mg BD
- Metformin 1 g BD
- Acarbose 100mg TID
Complaint of occasional ‘hypos’ if delay meals or moderate exertion. Relieved with snacks.
FPG 4.7 mmol/L; A1c 7.1%
Weight 72 kg (increased 3 kg since diagnosis)
Waist circumference 86 cm
Slide 10

Comment on her status?
What can we offer her?

- Hypos and weight gain with glibenclamide
- A1c not at target but FPG normal – most likely due to ‘snacking’
- Best option is to stop glibenclamide and replace with either glitazone or DPP4i → less ‘hypos’ → less ‘snacking’

Slide 11

Case 4

Mr A.Z., a 58-year-old Malay male, teacher
T2DM for 6 years
No complications
Currently on
Gliclazide MR 120 mg OM
Metformin 850mg BD
Acarbose 100mg tds
No ‘hypos’
FBS 7.4 mmol/L; A1c 7.8%
Weight 74 kg, waist circumference 88 cm
BMI 25kg/m²

Slide 12

Comment on his status.
How will you optimise his condition?

- Not obese
- Glycemic control not at targets (FPG & HbA1c) – patient is relatively young and no complications
- Best option is to add another oral agent – preferably DPP4i as cheaper than SGLT-2i and patient is not obese
Lecture Notes

TOPIC

7

insulin therapy & injectables
Background

- T2DM is a progressive disease characterised by worsening glycaemia due to progressive decline in beta cell function with subsequent failure of OADs to maintain long-term glycaemic control and insulin therapy will be required in the majority of patients.

- It is important to exclude chronic infections, malignancies or medications as a cause of poor glycaemic control.

- 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 oral antidiabetic agents or GLP-1 receptor agonists (GLP-1 RA).

Indications for insulin therapy in T2DM

Insulin therapy should be considered in the following situations:

- Inadequate glycaemic control on optimal dose and number of OADs

- As a short term use in the following:
  a) Acute illness or surgery
  b) Pregnancy
  c) Breast-feeding
  d) Severe metabolic decompensation (e.g DKA, HHS)

- As initial therapy in newly diagnosed type 2 diabetes
  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

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).

Types of insulin according to their pharmacokinetic profiles:

- **Prandial insulin** is administered pre-meal because of its short or rapid onset of action in controlling post-prandial glucose excursion.

- **Basal insulin** is administered once or twice daily and covers the basal insulin requirements in between meals and overnight.

- **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.
The time course of action may vary in different individuals, or at different time in the same individual. The variations and time periods indicated above should be considered as general guidelines only. The higher the dose of the insulin, the longer is the duration of action. The long acting insulin analogue, which has less peak, results in lower hypoglycaemic episodes and reduced weight gain compared to conventional insulin. At higher doses the long acting insulin analogue may have a significant peak. The rapid acting insulin analogues can be administered immediately before meals. Based on Cochrane reviews, insulin analogues are not superior to conventional human insulin in terms of efficacy other than reduced risk of symptomatic nocturnal hypoglycaemic events.
This can be done at the diabetic resource centre or via telephone calls. It should be done within the first few months of starting insulin.

**Intensification** - Modification of an insulin regimen to achieve better glycaemic control. Requires switching to more intensive insulin regimens for better glycaemic control.

**Starting an 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.
- 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.

**Comparison of Insulin Regimens Among Oral Treatment Failures**

![Graph showing comparison of insulin regimens on HbA1c and weight change](image)
### Slide 8

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

### Slide 9

**Optimising Insulin doses**

- Insulin dose optimisation requires gradual, safe and prompt titration of insulin dose according to SMBG.

- The insulin dose should be adjusted at least weekly within the first 3 months of starting insulin 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.

### Slide 10

**Switching insulin regimens – Intensification**

- Often the insulin regimens started may need modification if glycaemic control remains suboptimal despite dose optimisation.

- This requires switching to more intensive insulin regimens for better glycaemic control.

- This may entail increased number of injections.

- Insulin pump therapy may be considered in patients who are still not controlled while on basal-bolus regime.
Metformin should be continue while on insulin therapy unless contraindicated or intolerant. Sulphonylurea/meglitinides should be withdrawn once prandial insulin is used regularly with meals. DPP-4 inhibitors and SGLT2 inhibitors may be used in combination with insulin. Insulin dose should be optimised prior to switching/intensifying regimens.

Key elements for successful insulin intensification

- Patient’s education
- Dedicated diabetes team - diabetes educator, pharmacist, dietitian
- Self-blood glucose monitoring
- Frequent contact with healthcare team
- Support group
Monitoring Insulin Therapy

- Fasting Plasma Glucose (FPG)
- Glycosylated Hemoglobin (HbA1c)
- Self-monitoring of blood glucose (SMBG)

SMBG

- A tool which allows patients to evaluate their individual response to lifestyle, meals and therapy.
- Enables patients to assess whether glycaemic targets are being achieved. Able to depict glycaemic variability.
- SMBG is crucial in insulin self-titration and may help minimise hypoglycaemia.
- SMBG is both instrument and user-dependent. Involvement of a diabetes educator is key.

SMBG

- SMBG should be carried out at least 3-4 times daily in patients on multiple insulin injections or insulin pump therapy i.e. before each meal and before bed (10-11 pm)
- Once pre-prandial glucose targets are achieved, post-prandial glucose testing is recommended for fine-tuning of insulin therapy.
Pre-breakfast glucose readings reflect adequacy of pre-bed basal insulin. 
Pre-lunch readings reflect pre-breakfast short-acting insulin. 
Pre-dinner readings reflect pre-lunch short-acting insulin. 
Pre-bed readings reflect pre-dinner short-acting insulin. 
Post-prandial glucose readings reflect the adequacy of respective pre-meal rapid-acting insulin (analogs).

SMBG with use of Conventional Premixed Insulin 
Pre-breakfast glucose readings reflect the adequacy of intermediate-acting insulin. 
Pre-lunch readings reflect pre-breakfast short-acting insulin. 
Pre-dinner readings reflect pre-breakfast intermediate-acting insulin. 
Pre-bed readings reflect pre-dinner short-acting insulin.

SMBG with use of Premixed Insulin analogues 
Pre-breakfast glucose readings reflect the adequacy of long-acting insulin. 
Post-breakfast readings reflect pre-breakfast rapid-acting insulin. 
Post-lunch readings reflect pre-lunch rapid-acting insulin. 
Post-dinner readings reflect pre-dinner rapid-acting insulin.
**SLIDE 18**

**SMBG and Insulin Titration**

<table>
<thead>
<tr>
<th>To Control</th>
<th>Adjust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-breakfast Glucose</td>
<td>Pre-bed intermediate/long-acting insulin or pre-dinner premixed.</td>
</tr>
<tr>
<td>2-hours Post-breakfast Glucose</td>
<td>Pre-breakfast rapid-acting or premixed insulin analogue.</td>
</tr>
<tr>
<td>Pre-lunch Glucose</td>
<td>Pre-breakfast short-acting or premixed human insulin.</td>
</tr>
<tr>
<td>2 hours Post-lunch Glucose</td>
<td>Pre-lunch rapid-acting or pre-lunch premixed insulin analogue.</td>
</tr>
<tr>
<td>Pre-dinner Glucose</td>
<td>Pre-lunch short-acting or pre-breakfast premixed human insulin.</td>
</tr>
<tr>
<td>Post-dinner/Pre-bed Glucose</td>
<td>Pre-dinner rapid-acting or pre-dinner premixed insulin.</td>
</tr>
</tbody>
</table>

**SLIDE 19**

**General Guidelines for Long Term Use of Insulin (1)**

- The basal intermediate acting insulin should be administered pre-bed (preferably not earlier than 10pm) in view of of risk early morning hypoglycaemia if given earlier in the evening.
- It is not necessary to have an extra meal or snack after intermediate or long acting insulin.
- With high insulin requirements (>1.5 unit/kg per day), exclude conditions such as:
  - non-compliance
  - incorrect dosing or timing of injection
  - hypertrophy of injection sites
  - inter meal hypoglycaemia with rebound hyperglycaemia
  - expired insulin
  - occult infections

**SLIDE 20**

**General Guidelines for Long Term Use of Insulin (2)**

- 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.
**Slide 21**

Insulin Therapy - Recommendations

<table>
<thead>
<tr>
<th>Recommendations: Insulin Initiation, Optimisation and Intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The choice of insulin regimen should be individualised, based on the patient’s glycaemic profile, dietary pattern and lifestyle. (Grade C)</td>
</tr>
<tr>
<td>2. The biggest barrier is compliance and this should be adequately ascertained prior to any effort to intensify insulin therapy. (Grade C)</td>
</tr>
<tr>
<td>3. Optimisation of insulin therapy should be done within the first 3 months of insulin initiation. (Grade C)</td>
</tr>
</tbody>
</table>

---

**Slide 22**

Insulin Pump Therapy

- Continuous subcutaneous insulin infusion (CSI) or insulin pump therapy is another method to deliver insulin.
- Closely mimic normal physiological insulin profile.
- Utilises only fast acting insulin and eliminates the use of long-acting insulin.

---

**Slide 23**

Indications for insulin pump therapy in T2DM

- Inadequate glycaemic control with MDI (multiple daily injections) therapy
- Recurrent severe hypoglycaemia
- Hypoglycaemia unawareness
- Dawn phenomenon
- Gastroparesis
- Frequent diabetic ketoacidosis
Patient's Prerequisite for Insulin Pump Therapy

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

Non-insulin Injectables - GLP1 - RA

- If glycaemic targets have not been reached after optimal OAD therapy (provided A1c <10%), consider adding GLP-1 RA, as an alternative to intermediate or long acting insulin with less incidence of hypoglycaemia and weight gain.
- GLP1-RA is administered by subcutaneous injection.
- GLP-1 RA is not a substitute for insulin.
- GLP-1 RA should not be used in patients with a history of pancreatitis.
- GLP-1 RA should not be used if e-GFR <30 ml/min/1.73 m² (exenatide and lixisenatide) and e-GFR <60 ml/min/1.73 m² (liraglutide).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Minimum dose</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide IR</td>
<td>5 µg/20 µL, 10 µg/40 µL</td>
<td>5 µg BD</td>
<td>10 µg BD</td>
</tr>
<tr>
<td>Exenatide XR</td>
<td>2 mg</td>
<td>2 mg weekly</td>
<td>2 mg weekly</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>6 mg/mL</td>
<td>0.6 mg OD</td>
<td>1.8 mg OD</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>50 µg/mL, 100 µg/mL</td>
<td>10 µg OD</td>
<td>20 µg OD</td>
</tr>
</tbody>
</table>
**SLIDE 27**

**Exenatide**

- There are two formulations available: immediate release (IR) and extended release (XR).
- The IR formulation is given twice daily just before breakfast and dinner.
- The XR formulation is given weekly any time of day with or without meals.
- Exenatide IR formulation reduces A1c by 0.5–1.0% as add on to metformin and/or SU.
- Exenatide XR weekly in combination with OAD(s) reduces A1c up to 1.5%.

**SLIDE 28**

**Exenatide**

- Progressive weight loss is seen because of its effect on satiety and delay in gastric emptying.
- Main adverse effects are gastrointestinal symptoms, notably nausea which can be minimized by starting at a low dose with up-titration after a month.
- 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.

**SLIDE 29**

**Liraglutide**

- Once daily dose at any time of the day, same time every day.
- Indicated for use in combination with oral agents and insulin.
- A1c reductions of 0.8 to 1.4%.
- No increased risk of hypoglycaemia and may result in weight loss of 3.2 kg.
- 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.
- Gradual dose titration is important to minimise gastrointestinal side effects such as nausea, vomiting and diarrhoea.
Case Study

TOPIC 7

insulin therapy & injectables
Case 1

Madam Z.H., a 49-year-old Malay lady, an executive officer T2DM for 7 years, no complications.
Currently on Gliclazide MR 120mg OD, Metformin 1 g BD, Sitagliptin 100mg OD.
Usually has “lighter” breakfast and lunch; but tend to have late heavy dinner with family.
FPG 8-9 mmol/L; A1c 9%
SMBG pre-dinner 7-8 mmol/L; 2PPG 12-15 mmol/L

On Follow-up...

Weight 80 kg, BMI 32 kg/m², WC 90 cm
BP 140/90 mmHg
TG 4.5 mmol/L; HDL 0.9 mmol/L
She was re-counseled for change in lifestyle and insulin therapy.
She finally agreed for 1 injection per day.

Comment on her status. What can we offer her?
• In view of elevated post-dinner and pre-breakfast BG, option is to add single premixed insulin at dinner time and maintain OADs.
Case 2

Mr. M.Z., a 60-year-old Chinese male, retired teacher with T2DM for 10 years, complicated by peripheral neuropathy and immature cataract bilaterally.

Currently on Gliclazide 160 mg BD and Metformin 1 g BD.

FBS >13 mmol/L; A1c 10%.

Stopped SMBG; disappointed with the results which were always in the teens. Requesting for multivitamin to overcome lethargy and weight loss.

On Examination...

Weight 55 kg (was 60 kg 5 years ago)
WC 75 cm

Clinically euthyroid; BP 150/80 mmHg

Sensory loss in stocking distribution with no ulcer or wound or tinea pedis; dermopathy seen on the shins.

TG 1.8 mmol/L; LDL 3.4 mmol/L; HDL 1.3 mmol/L

24-hour urine protein 0.5 g per day.

Comment on his status. How will you optimise his condition?

- Weight loss and presence of multiple microvascular complications.
- Insulin therapy indicated to optimise glycaemic control.
- Need for eye assessment.
- Initiate basal insulin – start with low dose 0.2 u/ kg (10 units), monitor FPG and optimise dose till target pre-breakfast 4-6 mmol/L.
- If A1c still suboptimal despite normalisation of FPG then intensify insulin regimen.
**Case 3**

A 60-year-old lady, T2DM for 8 years.

Weight 83 kg, BMI 33 kg/m²

Difficulty controlling appetite

Medications:
- Metformin XR 2 g daily
- Gliclazide MR 90 mg OM

A1c 8.3%  FPG 7.2 mmol/L
SMBG post-meals: 10 – 15 mmol/L

**Case 3**

Hypertension on Perindopril 8mg daily, Amlodipine 10 mg daily.

Dyslipidemia LDL-C 2.7 mmol/L, HDL-C 0.9 mmol/L, TG 2.7 mmol/L on Simvastatin 40 mg ON

Urine ACR 5 mg/mmol
Eye review: Mild NPD bilateral
ALT 77iu/L, US Liver: Fatty changes
Symptoms of OSA

**Comment. What options of therapy?**

- Options to optimise therapy in obese patients.
- Importance to assess complications such as fatty liver and OSA.
- Appropriate selection of anti diabetic therapy with failure of metformin, SU – option of GLP1-RA should be discussed.
- Other options: Basal insulin in the morning
**Case 1**

52 year old truck driver, night drives
DM2 3+ years, Smoker, BMI 38, BP 164/92
Current meds:
metformin, gliiazide, pioglitazone, lovastatin, perindopril
HbA1c 10.1%, FBG 11.8 mmol/l, Chol 5.3, TG 3.1, eGFR 67

How would you change his medication?
Basal insulin (concern about hypo)
or
Liraglutide / exenatide (depending on shifts and eating pattern),
See dietitian,
Stop pioglitazone,
Change statin
Intensify BP Rx

---

**Exenatide vs Glargine – Effects on A1C and Weight**

Heine et al. Ann Intern Med 2005;143:559-569

---

**Exenatide vs Glargine in Type 2 Diabetes**

diabetes with hypertension
Hypertension & Type 2 Diabetes

- The prevalence of hypertension in T2DM worldwide is reported to be ~ 40-80%.
- From the National Diabetes Registry 2013, the prevalence was 70%.
- Hypertension should be detected and treated early in the course of DM to:
  - Prevent CVD
  - Delay the progression of renal disease and diabetic retinopathy

Diagnosis

- Prehypertension: 120–139/80–89 mm Hg
- Stage 1 hypertension: 140–159/90–99 mm Hg
- Stage 2 hypertension: ≥160/100 mm Hg
- Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >140/90 mmHg

Treatment Goals

- In general, the target blood pressure should be
  - Systolic < 135 mmHg
  - Diastolic < 75 mmHg
- Tight BP control should take precedence over the class of antihypertensive drug used.
- Combination therapy often required
- Lower BP target may be necessary to maximally protect against the development & progression of CV and renal disease.

Randomised clinical trials have demonstrated reduction of coronary heart disease (CHD) events, stroke and nephropathy when lowering SBP to <140 mmHg.
ADVANCE -
post trial ObservatioNal Study

BP Arm Results

Flow-chart for BP arm

BP levels: in-trial and post trial
(before and after stopping randomised treatment)

<table>
<thead>
<tr>
<th>BP arm</th>
<th>BP level (mmHg)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pre-randomization</td>
<td>145/81</td>
<td>145/81</td>
</tr>
<tr>
<td>Last randomized visit (after median of 4.4 years)</td>
<td>136/74</td>
<td>140/75</td>
</tr>
<tr>
<td>First ADVANCE-ON visit (a further 2.9 years later)</td>
<td>137/75</td>
<td>137/75</td>
</tr>
<tr>
<td>Final ADVANCE-ON visit (a further 3 years later)</td>
<td>137/74</td>
<td>138/75</td>
</tr>
</tbody>
</table>
Patients with hypertension should be advised to reduce their dietary sodium intake to no more than 2,000 mg per day; further reduction to 1,500 mg/day is desirable as it leads to even greater decreases in BP.
90% of patients require three antihypertensive medications to achieve target.
### Slide 13

<table>
<thead>
<tr>
<th>Concomitant Disease</th>
<th>Diuretics</th>
<th>β-blockers</th>
<th>ACEs</th>
<th>CCBs</th>
<th>Peripheral o-blockers</th>
<th>ARBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Non-diabetic renal impairment</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+*</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>+</td>
<td>+</td>
<td>+++$</td>
<td>+</td>
<td>+</td>
<td>+++$</td>
</tr>
<tr>
<td>Elderly with no co-morbid conditions</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Grading of recommendation (+ to ++++) is based on increasing levels of evidence; current widely accepted practice

+/- Use with care
- Contraindicated
* Only non-β-blocker/CRI CCB
$ Contraindicated in bilateral renal artery stenosis

### Slide 14

**Summary**

- Multi factorial approaches are needed for treatment of hypertension in patients with T2DM.
- Target BP goal <135/75 mmHg.
- ACE-I or ARB should be incorporated in the treatment.
- Fixed combination therapy is preferred in patients requiring more than one agent.
Case Study

diabetes with hypertension
Case

Mr. MK, a 55-year-old man.

T2DM and hypertension for 10 years. Medications:
Metformin 1 g bd
Gliclazide 160 mg bd
Amlodipine 10 mg daily

Referred for further management of poorly controlled diabetes and hypertension.

What are the possible causes for his poorly controlled diabetes and hypertension?

- Non-compliant to diet
- Non-compliant to treatment
- Hypoglycaemia?
- Underlying infections?
- Silent ischaemia?

- Social history: Salesman
  Frequent travelling
  On and off missed his medications
  Diet not controlled

- Family history: Mother – diabetic, on dialysis
  Father – stroke (residual left hemiparesis)
On examination:

- Obese
- Weight 98 kg, BMI 35 kg/m²
- BP 160/90 mmHg
- PR 88 beats/minute
- Bilateral proliferative retinopathy
- Minimal bilateral leg oedema
- Other systemic examination: unremarkable

Investigation results:

- A1c 9.2 %
- FBS 11.8 mmol/L
- Creatinine 106 µmol/L
- e-GFR 88 ml/min/1.73 m²
- 24h urinary protein 200 mg/24h
- ECG LVH

What are the issues that need to be addressed?

1. Poorly controlled diabetes with presence of microvascular complications
2. BP level not to target
3. Obesity could contribute to the poorly control diabetes and HPT
4. Need to explore any morbidities associated with the obesity (sleep apnoea, fungal infections etc)
Questions

What would be the A1c and BP target?

How would you manage him?

What would be the choices of anti-hypertensives or anti-diabetic agents?

Glycaemic Control
- Target A1c: ≤ 6.5%
- Add GLP1-receptor agonist or SGLT2-inhibitor
- Continue Metformin

Blood Pressure Control
- Target BP ≤ 135/75 mmHg (based on ADVANCE ON trial)
- Pharmacological approach:
  - add ARB: Irbesartan 150 mg daily (renoprotection)
- Non-pharmacological approach
  - sodium restriction
  - exercise
  - weight loss

ADVANCE-ON
post trial ObservatioNal Study

BP Arm Results
**Slide 10**

*Flow-chart for BP arm*

11,140 underwent randomisation into the blood pressure control arm

- 5,569 assigned to Active
  - 408 patients died
- 5,571 assigned to Placebo
  - 471 patients died

- 5,161 eligible for ADVANCE-ON
  - 884 non-participating patients and sites
  - 4,278 participated in ADVANCE-ON
- 5,100 eligible for ADVANCE-ON
  - 625 died
  - 1,048 no final visit
  - 2,638 at final visit, 2013

- N=10,261 (99%)

**Slide 11**

*BP levels: in-trial and post trial*

**(before and after stopping randomised treatment)**

<table>
<thead>
<tr>
<th>BP arm</th>
<th>BP level (mmHg)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Pre-randomization</td>
<td>145/81</td>
<td>145/81</td>
</tr>
<tr>
<td>Last randomized visit</td>
<td>136/74</td>
<td>140/75</td>
</tr>
<tr>
<td>First ADVANCE-ON visit</td>
<td>137/75</td>
<td>137/75</td>
</tr>
<tr>
<td>Final ADVANCE-ON visit</td>
<td>137/74</td>
<td>138/75</td>
</tr>
</tbody>
</table>

**Slide 12**

*Effects on Mortality*

- All cause mortality
  - Placebo
  - Perindopril-Indapamide
  - Relative risk reduction: p<0.001

- Cardiovascular death
  - Placebo
  - Perindopril-Indapamide
  - Relative risk reduction: p<0.001
IRMA 2 is a positive study, demonstrating a 70% risk reduction for the primary endpoint (prevention or slowing of progression to overt diabetic nephropathy), independent of the effects of irbesartan on systemic blood pressure.

A clear dose response is observed in IRMA 2 for the primary endpoint. The irbesartan 150 mg group demonstrates a 39% relative risk reduction (RRR) vs. the control group (placebo in addition to other non-excluded antihypertensive therapies) in the development of overt proteinuria (urinary albumin excretion rate [AER] > 200 µg/min, or 300 mg/day, and an increase of urinary AER from baseline by at least 30%), p=0.08. The irbesartan 300 mg group demonstrates a highly significant 70% RRR vs. the control group, p<0.001. The Kaplan-Meier curves separate at the first visit (at 3 months) and continue to diverge.

After adjustment for the baseline level of microalbuminuria and the achieved blood pressure during the study, the benefits of irbesartan in slowing progression to overt proteinuria are still present: RRR of 44% for irbesartan 150 mg vs. the control group (p=0.05); RRR of 68% for irbesartan 300 mg vs. the control group (p<0.001).
The event rates for the primary endpoint are approximately 15%, 10%, and 5% in the control (placebo in addition to other non-excluded antihypertensive therapies), irbesartan 150 mg, and irbesartan 300 mg groups, respectively. This corresponds to relative risk reductions of 39% for irbesartan 150 mg vs. the control group (p=0.08), and 70% for irbesartan 300 mg vs. the control group (p<0.001).

Two important secondary endpoints in IRMA 2 include change in overnight urinary albumin excretion rate (AER) and change in creatinine clearance. AER was reduced in the two irbesartan groups throughout the study (-24% and -38% at 24 months, compared with baseline, in the irbesartan 150 mg and 300 mg groups, respectively). AER remained unchanged in the control group (-2% at 24 months compared with baseline), p<0.001 for the comparison between the control group and the two irbesartan groups combined. Creatinine clearance remained in the normal range in all three groups throughout the study.

Regression to normoalbuminuria (< 20 µg/min, or < 30 mg/day) at the last visit was more frequent in the patients treated with irbesartan 300 mg than in the control (placebo in addition to other non-excluded antihypertensive therapies) group (34% vs. 21%, respectively, p=0.006).
Table 8 (A): Choice of antihypertensive drugs in diabetes patients with concomitant conditions (Adapted from Malaysian CPG for Hypertension 2008)

<table>
<thead>
<tr>
<th>Concomitant Disease</th>
<th>Diuretics</th>
<th>β-blockers</th>
<th>ACEIs</th>
<th>CCBs</th>
<th>Peripheral α-blockers</th>
<th>ARBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (without nephropathy)</td>
<td>+</td>
<td>+/-</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>DM (with nephropathy)</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
<td>+/+</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Gout</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>+/@</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Grading of recommendations (1 to ++++) is based on increasing level of evidence: 1. current widely accepted practice
2. Guideline recommend
3. Recommendation
4. Only non-dihydropyridine CCBs

Take Home Messages

- Target A1c ≤ 6.5%
- Target BP ≤ 135/75 mmHg
- Most patients with hypertension will require two or more antihypertensive agents to achieve their BP goals
- Pharmacological treatment should comprise a regimen that includes either an ACEI or an ARB as first line.
diabetes with dyslipidaemia
People with Type 2 diabetes have a higher risk of myocardial infarction (MI) than non-diabetic individuals. In one study, people with Type 2 diabetes who had never had an MI had as high a risk of having one as people without Type 2 diabetes with a history of MI.

DM is a coronary heart disease (CHD) risk equivalent. Control of hyperglycaemia in T2DM has not been associated with significant decrease in CVD events except in overweight people with diabetes who were given metformin. In other people with T2DM the effect of hyperglycemia treatment on macrovascular complication can only be seen after 15-18 years early aggressive therapy. Thus, efforts must also be directed to control other risk factors such as dyslipidaemia, hypertension and other new emerging risk factors.

Reference
TREATING THE ABCS REDUCES DIABETIC COMPLICATIONS

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose control</td>
<td>Heart attack</td>
<td>↓ 37%</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>↓ 61%</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>↓ 66%</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>↓ 44%</td>
</tr>
<tr>
<td></td>
<td>Diabetes-related death</td>
<td>↓ 32%</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>Coronary heart disease mortality</td>
<td>↓ 55%</td>
</tr>
<tr>
<td></td>
<td>Major coronary heart disease event</td>
<td>↓ 55%</td>
</tr>
<tr>
<td></td>
<td>Any atherosclerotic event</td>
<td>↓ 37%</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease event</td>
<td>↓ 63%</td>
</tr>
</tbody>
</table>


HPS: Statin Therapy Beneficial Among Patients with Diabetes

<table>
<thead>
<tr>
<th>SIMVASTATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Rate ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>999 (23.5%)</td>
<td>1250 (28.4%)</td>
</tr>
<tr>
<td>Other CHD (not MI)</td>
<td>460 (18.6%)</td>
<td>591 (24.2%)</td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>172 (18.7%)</td>
<td>212 (23.6%)</td>
</tr>
<tr>
<td>PVD</td>
<td>327 (24.7%)</td>
<td>420 (30.5%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>276 (13.8%)</td>
<td>367 (18.8%)</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2033 (19.9%)</td>
<td>2585 (25.2%)</td>
</tr>
</tbody>
</table>

HPS = Heart Protection Study

2.4% reduction (P=0.00001)

HPS Lancet 2002;301:7-22

CARDS: Effect of Statin for PRIMARY Prevention in DM

- n = 2838
- Age 40-75, no history of CVD
- T2DM plus one or more:
  - Retinopathy
  - Albuminuria
  - Hypertension
  - Smoking
- Intervention: Atorvastatin 10 mg vs. Placebo
- Outcome: ACS, revascularization, stroke

CARDs: Statins Reduced CVD in Patients with DM

<table>
<thead>
<tr>
<th>Number of patients with an event (%)</th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>127 (9.0%)</td>
<td>83 (5.8%)</td>
<td>0.63 (0.48–0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5%)</td>
<td>51 (3.6%)</td>
<td>0.64 (0.45–0.90)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td>34 (2.4%)</td>
<td>24 (1.7%)</td>
<td>0.69 (0.41–1.16)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.8%)</td>
<td>21 (1.5%)</td>
<td>0.52 (0.31–0.88)</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>82 (5.8%)</td>
<td>61 (4.3%)</td>
<td>0.73 (0.52–1.01)</td>
<td>0.059</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>189 (13.4%)</td>
<td>134 (9.4%)</td>
<td>0.68 (0.55–0.83)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


Who Should Receive Statins?
(regardless of baseline LDL-C)

- ≥40 yrs old  or
- Macrovascular disease  or
- Microvascular disease  or
- DM >15 yrs duration and age >30 years  or

Among women with childbearing potential, statins should only be used in the presence of proper preconception counseling & reliable contraception. Stop statins prior to conception.

What if baseline LDL-C ≤2.0 mmol/L?

- Within CARDs and HPS, the subgroups that started with lower baseline LDL-C still benefited to the same degree as the whole population

- If the patient qualifies for statin therapy based on the algorithm, use the statin regardless of the baseline LDL-C and then target an LDL reduction of ≥50%

**Slide 9**

The epidemiological and interventional relationships of cholesterol, blood pressure and HbA1c with cardiovascular disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHD (fatal and non-fatal MI and sudden death)</th>
<th>Cardiovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (1mmol/l or 39 mg/dl)</td>
<td>-30</td>
<td>44.4</td>
</tr>
<tr>
<td>Epidemiological (%)</td>
<td>-23</td>
<td>59.2</td>
</tr>
<tr>
<td>Intervention (%)</td>
<td>-23</td>
<td></td>
</tr>
<tr>
<td>NNT for 5 years</td>
<td>59.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Blood pressure (10/5 mmHg)</td>
<td>-25</td>
<td>61.8</td>
</tr>
<tr>
<td>Epidemiological (%)</td>
<td>-22</td>
<td>33.6</td>
</tr>
<tr>
<td>Intervention (%)</td>
<td>-22</td>
<td></td>
</tr>
<tr>
<td>NNT for 5 years</td>
<td>61.8</td>
<td>33.6</td>
</tr>
<tr>
<td>Glycemia (HbA1c 0.9%)</td>
<td>-12</td>
<td>140.3</td>
</tr>
<tr>
<td>Epidemiological (%)</td>
<td>-9.7</td>
<td>118.5</td>
</tr>
<tr>
<td>Intervention (%)</td>
<td>-9.7</td>
<td></td>
</tr>
<tr>
<td>NNT for 5 years</td>
<td>140.3</td>
<td>118.5</td>
</tr>
</tbody>
</table>

NNT = number needed to treat

Yaqoob Z et al. Diabetesologia 53:2076-2085, 2010

**Slide 10**

Dyslipidaemia & Diabetes: Screening

- In adult patients, test for lipid disorders at least annually
- More often if needed to achieve the goal
- In children and 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 two years.

**Slide 11**

Primary target: LDL Cholesterol

In individuals without overt CVD:
- All patients over the age of 40 years should be treated with a statin regardless of baseline LDL cholesterol levels

In individuals with overt CVD:
- All patients should be treated with a statin.
- The target of LDL cholesterol: 1.8 mmol/L.
SLIDE 12

Secondary Target: Non-HDL, HDL & TG

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL cholesterol</td>
<td>&lt; 3.4 mmol/L</td>
</tr>
<tr>
<td></td>
<td>(when TG &gt; 2.3 mmol/L)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&gt; 1.0 mmol/L for males</td>
</tr>
<tr>
<td></td>
<td>&gt; 1.2 mmol/L for females</td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 1.7 mmol/L</td>
</tr>
</tbody>
</table>

SLIDE 13

Non-Pharmacological Treatment

- 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.

SLIDE 14

Pharmacological Treatment

<table>
<thead>
<tr>
<th>Lipid Goal</th>
<th>Initial Drug</th>
<th>Suggested addition (in order of preference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL cholesterol</td>
<td>Statins</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>Increase HDL cholesterol</td>
<td>Fibrates</td>
<td></td>
</tr>
<tr>
<td>Lower TG</td>
<td>Fibrates or nicotinic acid</td>
<td>Statins</td>
</tr>
<tr>
<td>Treat combined hyperlipidaemia</td>
<td>Statins</td>
<td>Fibrates Resin plus Fibrates Nicotinic Acid</td>
</tr>
</tbody>
</table>
Pharmacological Treatment (cont.)

- In T2DM with very high TG, reduction of carbohydrate intake is emphasised.
- Lowering TG in patients with clinical CVD and normal LDL-cholesterol with a fibrate is associated with a reduction in cardiovascular events.
- Combination therapy using simvastatin and ezetimibe has helped to achieve lipid targets more than simvastatin alone and this has resulted a further 7.6% reduction in CVD events compared with simvastatin alone.

Pharmacological Treatment (cont.)

Special situations

- Statin therapy is contraindicated in pregnancy.
- Treatment strategies in children and adolescents are no different with regards to dietary and glycaemic control.
- Lipid lowering medications should only be initiated in those >10 years old.

Recommendations

- All patients without overt CVD over the age of 40 years should be treated with a statin regardless of baseline LDL cholesterol levels.
- All patients with overt CVD should be treated with a statin and if LDL target not achieved, combination with ezetimibe is recommended.
Case Study

diabetes with dyslipidaemia
**Case**

A 58-year-old Indian man has a 7-year history of T2DM. He was admitted with acute myocardial infarction a year ago and angioplasty was done with 2 stents inserted. He is a manager with a sedentary lifestyle. He was smoking 20 cigarettes/day until a year ago. No alcohol. 

Medications:

- Gliclazide 160 mg bd
- Metformin 850 mg bd
- Ramipril 5 mg/day
- Bisoprolol 5 mg/day
- Clopidogrel 75 mg/day
- Aspirin 150 mg/day
- Atorvastatin 40 mg/day

**On examination:**

Weight 74 kg; Height: 1.67 m, BMI: 27.9 kg/m²

BP 130/80 mmHg. Haemodynamically stable.

Mild peripheral neuropathy in the toes bilaterally. Foot pulses are both present.

**Investigation results:**

Creatinine 92 umol/L, e-GFR >60 ml/min/1.73 m²

A1c: 7.2%

TChol: 4.6 mmol/L; TG: 1.8 mmol/L; HDL-C: 1.0 mmol/L; LDL-C: 2.42 mmol/L

Thyroid function: NAD

LFT: NAD
What should be next course of action?

- Patient counselled regarding diet and exercise.
- Compliance of medications emphasised.
- Stop smoking.
- Add ezetimibe 10 mg od.

3 months later

Weight 72 kg
A1c 6.9%
TChol: 4.5 mmol/L; TG: 1.3 mmol/L; HDL-C: 1.1 mmol/L; LDL-C: 1.83 mmol/L
diabetes with obesity
Objectives of presentation

- 1. Classifications of weight by BMI.
- 2. Anti diabetic agents and effects on weight
- 3. Non Pharmacological treatment of obesity
- 4. Pharmacological treatment of obesity
- 5. Role of Bariatric surgery


Classification of Weight By BMI

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th><strong>Risk of co-morbidities (T2DM, HPT, CVD)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Low (but increased risk of other clinical problems)</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 22.9</td>
<td>Optimal</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI ≥ 23.0</td>
<td></td>
</tr>
<tr>
<td>Pre-Obese</td>
<td>23.0 – 27.4</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese I</td>
<td>27.5 – 34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obese II</td>
<td>35.0 – 39.9</td>
<td>Very high</td>
</tr>
<tr>
<td>Obese III</td>
<td>≥ 40</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>
How is obesity managed in patients with diabetes?

Medical Complications of Obesity

Obesity

Biomechanical
- Dismotility/disability
- GERD
- Lung function defects
- Osteoarthritis
- Sleep apnea
- Urinary incontinence

Cardiometabolic
- Dyslipidemia
- Hypertension
- Prediabetic states
- NAFLD
- PCOS

Diabetes

Cardiovascular Disease

Other
- Androgen deficiency
- Cancer
- Gallbladder disease
- Psychological disorders

GERD: gastroesophageal reflux disease. NAFLD: nonalcoholic fatty liver disease. PCOS: polycystic ovary syndrome.

By Dr. John Doe, 2020

Weight Loss Reduces Cardiometabolic Risk Factors in Patients With Type 2 Diabetes

Unmetabolic Lifestyle Intervention, 8.6% Weight Loss
Diabetes Support and Education, 8.7% Weight Loss

Blood glucose, cholesterol, and systolic blood pressure were significantly lower in the intervention group compared to the control group. P<0.05 between groups.
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.

### Anti-Diabetic Agents and Their Effects on Weight

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Metformin</td>
<td>GLP-1 RA</td>
</tr>
<tr>
<td>TZDs</td>
<td>AGI</td>
<td>SGLT 2 Inhibitors</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>DPP-4 Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment of Overweight and Obesity

- Goal of therapy is to achieve optimal glycaemic and metabolic control through lifestyle modifications and behavioural change, physical activity and dietary restrictions.

- Non pharmacological interventions includes**
  - Dietary: Calorie restrictions of 1200 to 1500 kcal/day.
  - Increased physical activity about 250 to 300 minutes per week of moderate-intensity.
  - Weight loss of between 5-10% will improve glycemic control, blood pressure, lipid profile and quality of life.

- **Should be the mainstay of treatment.

### Pharmacotherapy for Obesity

When to start Anti Obesity?

- Diabetic patients with BMI of ≥ 27.0 kg/m² and failed 6 months of lifestyle modifications.
In Malaysia, 2 anti-obesity agents have been approved, Phentermine and Orlistat. Phentermine only indicated for short term - 3 months.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Drug Class</th>
<th>MOA for Weight loss</th>
<th>Duration</th>
<th>Net Weight loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duramine (Phentermine)</td>
<td>Sympathomimetic amine</td>
<td>Appetite Suppression</td>
<td>26 weeks</td>
<td>3.6</td>
</tr>
<tr>
<td>Orlistat (Xenical)</td>
<td>Lipase Inhibitor</td>
<td>Reduced gastrointestinal fat absorption</td>
<td>4 years</td>
<td>6.9</td>
</tr>
<tr>
<td>Topiramate/Phentermine</td>
<td>Anticonvulsant/sympatho-mimetic amine</td>
<td>Appetite suppression, altered satiety action</td>
<td>56 weeks</td>
<td>8.8</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Serotonin 5HT2C RA</td>
<td>Appetite suppression</td>
<td>52 weeks</td>
<td>4.8</td>
</tr>
<tr>
<td>Bupropion/Naltrexone</td>
<td>Antidepressant/opioid RA</td>
<td>Appetite suppression, altered satiety action</td>
<td>48 weeks</td>
<td>6.2</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 RA</td>
<td>Slows gastric motility, reduced satiety</td>
<td>20 weeks</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56 weeks</td>
<td>5.8</td>
</tr>
</tbody>
</table>

When to Refer for Bariatric Surgery?

- Recommended after lifestyle and pharmacological interventions failed in severely obese diabetic patients.
- The Asian Consensus Meeting on Metabolic Surgery (ACMOMS) recommends bariatric surgery for the following:
  - Diabetic patients > 32 kg/m²
  - Diabetic patients > 30 kg/m² with 1 or more features of metabolic syndrome.

Criteria for Bariatric Surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss History</td>
<td>Failure of previous nonsurgical attempts at weight reduction, including nonprofessional programs (e.g. weight watchers)</td>
</tr>
<tr>
<td>Commitment</td>
<td>Expectation that patient will adhere to postoperative care:</td>
</tr>
<tr>
<td></td>
<td>- Follow up visits with healthcare team.</td>
</tr>
<tr>
<td></td>
<td>- Compliance to medical management.</td>
</tr>
<tr>
<td></td>
<td>- Continued dietary restrictions.</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>BMI &lt; 30 kg/m².</td>
</tr>
<tr>
<td></td>
<td>- Current drug or alcohol abuse.</td>
</tr>
<tr>
<td></td>
<td>- Uncontrolled, severe psychiatric illness.</td>
</tr>
<tr>
<td></td>
<td>- Lack of comprehension of risks, benefits, expected outcomes, alternatives and required lifestyle changes.</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGE

• Careful choice of anti diabetic to minimise weight gain and without compromising glycaemic control.
• Lifestyle measures remain the cornerstone of treatment.
• Anti obesity can be considered after lifestyle modifications initiated.
• Bariatric surgery may hold promise for selected patients.
Case Study

diabetes with obesity
Case 1
A 48-year old bank clerk suffers from diabetes for the last 5 years.
He was referred for diabetes control and morbid obesity
Currently he is treated with Metformin 850 bid + Gliclazide 160 mg bid.
Weight 112 kg Ht 165 cm BMI = 41.2
Has 3 meals daily with a heavy lunch.
Does not look after his diet and hardly exercise. No SBGM.

Other Med Hx:
Hypertension (on a combination of amlodipine 10 mg bid, perindopril 8 mg OD and nitritilia 1 tab OD)
Hyperlipidemia (20 mg rosvastatin )
Snores heavily and being investigated for sleep apnea by respi. unit

Case 1 (con’t)
His A1c for the last 6 months were 8.5 % and 8.8 % respectively.
FBG was 9.1 mmol/l
Chest physician tried Acarbose 100 mg tid but he developed bad colic and flatulence. Doctor made a note that patient is not motivated to loose weight
Nevertheless he was also referred to the dietician to loose weight and control his diabetes.

BP 142/85 HR 92/min
UFEME prot 2+
TC: 4.9 mmol/l
TG: 2.3 mmol/l
HDL: 0.6 mmol/l
LDL: 3.2 mmol/l

Questions:
1. How would you bring down his glucose levels?
2. How would your choice of therapy influence his other co-morbidities?
3. Give reasons for choosing this form of therapy
What is your course of action?

1. Increase the metformin to tid
2. Bedtime intermediate insulin
3. Mixed insulin bid
4. Basal bolus regime
5. GLIP analogue

---

Comparison of Insulin Regimens Among Oral Treatment Failures

- Mirtapat/NA (N= 32)
- Saxing/NA (N= 28)
- Two daily injections (N= 29)
- Multiple daily injections (N= 30)
- Control (N= 30)

<table>
<thead>
<tr>
<th>Change in HbA1c (%)</th>
<th>Weight Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>-1.9</td>
<td>1.2*</td>
</tr>
<tr>
<td>-1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>0.5</td>
<td>2.2*</td>
</tr>
<tr>
<td>0.9</td>
<td>2.9*</td>
</tr>
</tbody>
</table>

*P < 0.001 vs. control group
†P < 0.05 vs. other insulin treatment groups

---

Case 1 (2 months later)

He was finally convinced to start on bedtime insulinard at 16 units which was gradually titrated to 28 units. The dose of gliclazide was reduced to 80 mg bid and attempt to increase metformin to tid failed.

FBG came down to 8.2 mmol/l
A1c reduced to 10.3
Weight went up to 116 kg
Patient is not too happy with the weight gain
Helping Patients Lose Weight

**Acknowledge that:**
- Obesity is a disease\(^a\)
- Environment influences obesity\(^b\)
- Weight loss is a process
- Help is available

\(^{a}\) American Medical Association\(^{[14]}\)

Individualizing Weight Loss Treatment\(^a\)

- Determine BMI
- Measure waist circumference
- Consider comorbid conditions in determining treatment
- Ask about medications and adjust those associated with weight gain\(^b\):
  - Antidiabetic agents (insulin, sulfonylureas, thiazolidinediones)
  - Psychotropic medications
  - Steroids
  - Antihistamines
  - \(\beta\)-blockers

\(^{a}\) National Institutes of Health\(^{[21]}\)
\(^{b}\) Leslie WS, et al. QJM. 2007;100:395-404\(^{[29]}\)

Individualizing Weight Loss Treatment (cont)

- **Assess the patient’s obesity-associated risk:**
  - High BMI with weight-related comorbidities: Consider bariatric surgery
  - Low BMI with no weight-related comorbidities: Consider diet/behavioral change before medication

- **Consider other patient factors**
  - Health insurance coverage and affordability of treatment
  - Literacy level
  - Social environment and family support
  - Access to transportation
  - Access to commercial weight loss programs or other community resources

National Institutes of Health\(^{[22]}\)
The 5 As*

1. **Ask**: As the first step, ask the patient if it is alright to talk about their weight; this demonstrates respect and helps reduce stigma.
2. **Advise**: Deliver clear, strong, personal, and straightforward advice about the importance of obtaining a healthy weight.
3. **Assess**: Determine the patient’s preparedness to work on weight control.
4. **Assist**: Provide strategies for weight management.
5. **Arrange**: Set follow-up appointment(s) or referral(s) to other resources.

*Adapted from strategies for smoking cessation.


---

Assessing Patient Readiness and Resources

- Reasons and motivation for weight loss
- Potential barriers to adopting change
- Time availability
- Understanding of risks and benefits
- Support expected from family and friends
- Weight loss goals

National Institutes of Health.

---

Assessing Patient Readiness for Weight Loss

- How important is it for you to get your weight under control?

<table>
<thead>
<tr>
<th>Not important</th>
<th>Very important</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

- How confident are you that you can get your weight under control?

<table>
<thead>
<tr>
<th>Not confident</th>
<th>Very confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>
Set Realistic Goals

- Short-term goal: 5% to 10% loss at 6 months
- Interim goal: maintenance
- Long-term goal (if desired): additional energy deficit recalculated for next weight loss goal

Questions:

Further questioning revealed a diet high in CHO and low in fat. He was advised to cut 500kcal from his daily calories by the dietician. This was not followed. He did not acquire the stationary cycle that he was asked to purchase. Discussion with dietician to reduce his intake further to 800-1500 kcal was deemed impractical.

He has not started on CPAP for his OSA.
Still contemplating

What would you do now?

Course of action;

1. Commercially prepared meal replacement
2. A 6-month trial of orlistat
3. A 4-6 month trial of phentermine
4. SGLT2 inhibitor
5. Incretin mimetic or GLIP analogue
6. Admit for Very Low Calorie Diet (VLCD)
7. Refer for bariatric surgery
Progress

He was started on free trial of liraglutide 0.6 mg mane and gradually increased to 1.2 mg daily. The bedtime insulatard was continued.

Off label use of GLIP and insulin

He was warned of possible hypoglycaemia

Case 1 (1 month later)

His A1c came down to 8.4%
FBG 7.6 mmol/l
Weight came down to 112 kg

It is important that patients who are started on weight reducing agents that they are reviewed a month later as a means to determine response to treatment (and not leave them on the agent for months)

Practice Point

We are able to determine if patients will respond to treatment to anti-obesity agents esp GLIP-1 RA within a month (criteria: weight lost > 1 kg in the first month)

Selecting Treatment for Obesity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>&lt; 24.9</th>
<th>25-26.9</th>
<th>27-29.9</th>
<th>30-35</th>
<th>35-39.9</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, exercise, behavior therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>With comorbidities</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With comorbidities</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>With comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Source: The Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults
A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Mass Index category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, physical activity, and behavior therapy</td>
<td>25-26.9</td>
</tr>
<tr>
<td></td>
<td>27-29.9</td>
</tr>
<tr>
<td></td>
<td>30-34.9</td>
</tr>
<tr>
<td></td>
<td>35-39.9</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
</tr>
<tr>
<td>With co-morbidity</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Pharmacotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Mass Index category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-26.9</td>
</tr>
<tr>
<td></td>
<td>27-29.9</td>
</tr>
<tr>
<td></td>
<td>30-34.9</td>
</tr>
<tr>
<td></td>
<td>35-39.9</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
</tr>
<tr>
<td>With co-morbidity</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Mass Index category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-26.9</td>
</tr>
<tr>
<td></td>
<td>27-29.9</td>
</tr>
<tr>
<td></td>
<td>30-34.9</td>
</tr>
<tr>
<td></td>
<td>35-39.9</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
</tr>
<tr>
<td>With co-morbidity</td>
<td>+</td>
</tr>
</tbody>
</table>

2013 AHA/ACC/ATS Guideline for the Management of Overweight and Obesity in Adults. http://circ.ahajournals.org/content/116/1/e49 do 000437397.8477 nx citation

Pharmacologic Treatment for Obesity

- Not considered replacements for lifestyle changes
- Serve as adjuncts to diet and exercise
- Generally used long-term to manage and help maintain weight loss
- Can be tailored to meet individual patient needs
management of diabetic emergencies 1
Hypoglycaemia

Definition

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

Symptoms of Hypoglycaemia

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

Severity of Hypoglycaemia

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

A major complication of hypoglycaemia is an increased risk of cardiac arrhythmia. Abnormal, prolonged cardiac repolarization with an increase in QTc and QTd has been observed in studies.¹

As previously shown, declining plasma glucose levels trigger physiologic defenses, including a decrease in pancreatic beta-cell insulin secretion. Increases in pancreatic beta-cell glucagon and adrenomedullary epinephrine secretion also normally occur.¹

Sustained, severely low glucose levels can cause neuroglycopenic symptoms. Without treatment, these low levels can lead to cognitive impairment, seizure, coma, and brain death.²

---

Severe Hypoglycemia May Cause a Prolongation of QT Interval in Patients With Type 2 Diabetes

Landstedt-Hallin et al.¹ examined the effect of insulin-induced hypoglycaemia on cardiac repolarization in 13 patients with type 2 diabetes. All patients had been treated with both insulin and oral glibenclamide for at least 8 months before the start of the study. The patients stopped using oral glibenclamide for 2 weeks but continued with insulin therapy. They were subjected to a first hypoglycemic clamp at the end of these 2 weeks. The patients then resumed combined glibenclamide and insulin therapy, and after 6 to 8 months they participated in a second hypoglycaemic clamp. Eight patients were subjected to a third
As demonstrated in the graph, the study showed that mean QT intervals and QT dispersion were significantly prolonged after the hypoglycaemic clamps. These results showed that hypoglycaemia affected repolarization of the myocardium, creating an increased risk of arrhythmias.\(^{1}\)

**Slide 9**

**Asymptomatic Episodes of Hypoglycemia May Go Unreported**

In clinical studies of continuous glucose monitoring (CGM), episodes of hypoglycaemia have been found to go unrecognized.\(^{1-3}\)

Chico et al\(^{1}\) used CGM to measure the frequency of unrecognized episodes of hypoglycaemia in patients with type 1 (n=40) and type 2 (n=30) diabetes. CGM detected unrecognized hypoglycaemic events in 55.7% of all patients. In the subset of patients with type 2 diabetes, CGM detected hypoglycaemic events in 46.6% of patients.\(^{1}\)

Other researchers have reported similar findings.\(^{2,3}\)

**Slide 10**

**Sleep blunts the counter-regulatory catecholamine response to hypoglycaemia**

Sleep decreases the epinephrine response to hypoglycaemic events in patients with T1DM and the warning signs of hypoglycaemia are reduced.

Jones study: Epinephrine response was measured in adolescents with T1DM (n=8) and age-matched controls (n=6) in daytime and nighttime in response to insulin-induced hypoglycaemia. In each study, the plasma glucose concentration was stabilised for 60 min at
approximately 100 mg/dL and then reduced to 50 mg/dL for 40 min at various time points. On the x-axis represents the beginning of the hypoglycaemic period. In both healthy participants and patients with T1DM, epinephrine response was blunted while they were asleep, and maintained while they were awake in daytime. When patients with T1DM were awake at night, the epinephrine response was maintained.

**Slide 11**

**Hypoglycemia Outcomes**

**VADT, ACCORD, ADVANCE**

**VA Database Review of Coded Hypoglycemia Versus Subsequent CVD Events**

**Hypoglycemia: A Nuisance or an Important Contributor to Mortality?**

**Slide 12**

**Hypoglycemia and Weight Gain are linked**

**Hypoglycemia leads to Defensive eating**
**Slide 13**

**Hypoglycaemia in T2DM:**

*Possible mechanisms:*

- Neuroendocrine changes:
  - Activation of autonomic nervous system
  - 10-100-fold increased secretion of adrenaline & noradrenaline
- GI changes:
  - Longer GI transit
- Hypokalaemia
- Hypoglycaemic changes:
  - Platelet activation
  - Increased viscosity

\*P < 0.01 vs episodes during hyperglycaemia and normoglycaemia, HbA1C blood glucose levels, T2DM-type 2 diabetes mellitus.

**Study of T2D continuous glucose monitoring and simultaneous cardiac rhythm monitoring in patients with T2DM treated with insulins and history of frequent hypoglycaemia and coronary artery disease (n=38). 54 episodes of hypoglycaemia reported (BG <3.9 mmol/l).**


- **Symptoms of Hypoglycaemia:** ↑ medication non-adherence by 76% \(^1\)
- **Hypoglycaemia makes clinicians less likely to implement glycaemic targets** \(^2\)

\(^1\)Diabetes Research & Clinical Practice 87 (2010) 204–210
\(^2\)Cyrer PF. Diabetesologia. 2002; 45: 937–948.

---

**Slide 14**

**Risk factors for hypoglycaemia:**

- Advancing age
- Severe cognitive impairment
- Poor health knowledge
- Increased A1c
- Hypoglycaemia unawareness
- Long standing insulin therapy
- Renal impairment, Neuropathy

---

**Slide 15**

**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.
Evidence suggests that 15 g of glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people.
The aims of treatment are to:

- Detect and treat a low blood glucose level promptly.
- Eliminate the risk of injury to oneself and to relieve symptoms quickly.
- Avoid overcorrection of hypoglycaemia especially in repeated cases as this will lead to poor glycaemic control and weight gain.

Treating hypoglycemia: 3 steps

1. Give 15 g of glucose or fast-acting carbohydrate-containing food.
2. Wait 15 minutes.
3. Recheck BG levels—give another 15 g if necessary.

- Equivalents to any one of the following:
  - 4 oz (1/2 cup) fruit juice or nonfat soda
  - 6 oz (1 cup) low-fat milk
  - 3 glucose tablets
  - 1 tablespoon honey, brown sugar, or corn syrup
  - If patient cannot take anything orally, give 25 mL of D50 as an IV push, if no IV access, give glucose 1 mg/mL

Avoid overtreatment (excessive amount of glucose), which may result in significant hyperglycaemia within the next 4-6 hours.

- In severe hypoglycaemia where the individual is still conscious:
  - Ingest 20 grams of carbohydrate and the above steps are repeated.

- In severe hypoglycaemia and unconscious individual:
  - He/she should be given IV 20–50 mL of D50% 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 on:
  - strategies for prevention,
  - recognition, and
  - treatment of hypoglycaemia.

- Individuals on insulin may need to have their insulin regimen adjusted appropriately to lower their risk.
Case Study

management of diabetic emergencies 1
Case 1

- A 76-year-old female patient was admitted to the orthopedic unit for right hip replacement.
- She has diabetes for 15 years and had been treated with glibenclamide (glyburide) 5 mg twice daily and metformin 1 g/day.
- In the morning of the admission day and after she had taken her diabetes medications at home, she complained of nausea, vomiting, and diarrhoea and refused any food intake.

Case 1

- In the afternoon the patient was found comatose in bed.

  - What is the possible reason for her unconsciousness?

  - What would you do?

Case 1

- Computed tomography of the brain was normal.
- Blood was sent to the laboratory for biochemical analysis; after about 2 hours the laboratory informed the unit that the patient's blood glucose was 20 mg/dL (1.1 mmol/L).
Case 1

- What was wrong with this patient?
- Glibenclamide (glyburide) is a well-known sulphonylurea that may cause severe hypoglycemia more often than other sulphonylureas due to the prolonged duration of action of the medication and its metabolites.
- The relatives should have been informed about the risk of hypoglycaemia with glibenclamide (glyburide) and they should have informed the personnel of the unit that the patient had taken her medications before admission.

Case 1

- Blood glucose should have been closely monitored in the hospital and, if it was low, intravenous glucose infusion should have begun.
- In addition, every unconscious patient should be considered as hypoglycaemic, especially if the patient has diabetes, until immediate estimation of the blood glucose levels rules out hypoglycaemia. Thus the patient should have been managed as having been in hypoglycaemic coma until the results of the blood test were available.

Case 1

- How will you manage this patient?
- The patient was unconscious, thus a bolus of 20-50 ml of 50% glucose solution or 50 ml of 35% glucose solution, followed by infusion of 10-20% glucose solution should begin with frequent monitoring of blood glucose.
Slide 7

Pathophysiology: Hierarchy and thresholds of physiological mechanisms involved in the response to low blood glucose level

Slide 8

Hypoglycaemic Symptoms Based on Blood Glucose Levels

Slide 9

In severe hypoglycaemia where the individual is still conscious:
- ingest 20 grams of carbohydrate and the above steps are repeated.

In severe hypoglycaemia and unconscious individual:
- He/she should be given IV 20–50 mL of D50% over 1–3 minutes.
- Outside the hospital setting, a tablespoon of honey should be administered into the oral cavity.
management of diabetic emergencies 2
Diabetic Ketoacidosis

- Most serious acute complications.
- High mortality rate if unrecognised. The overall mortality is <1%, mortality rate >5% in the elderly.
- Precipitating factors: infection, missed therapy, acute coronary syndrome, CVA, surgery etc.
- Diagnostic criteria: (All three must be met)
  - Capillary blood glucose >11 mmol/L
  - Capillary ketones >3 mmol/L or urine ketones ≥2+
  - Venous pH <7.3 and/or bicarbonate <15 mmol/L

High Dependency Unit Care

- High-dependency unit (HDU) admission and insertion of central line in the following circumstances:
  - Elderly
  - Pregnant ladies
  - Heart or kidney failure
  - Other serious comorbidities
  - Severe DKA

Criteria For Severe Ketoacidosis

- Venous bicarbonate <5 mmol/L
- Blood ketones >6 mmol/L
- Venous pH <7.1
- Hypokalaemia on admission (<3.5 mmol/L)
- Glasgow Coma Scale (GCS)<12
- Oxygen saturation <92% on air (arterial blood gases required)
- Systolic BP <90 mmHg
- Pulse >100 or < 60 beats/minute
Principles Of Management – 1st Hour

1st Hour: Immediate Management

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

Step 2. Commence a fixed rate intravenous insulin infusion (FRI) 0.1 U/kg/hour based on estimate of weight. 5U/ml short acting human insulin added up to 80 ml with 0.9% saline solution.

Step 3. Assess patient

- BP
- Pulse
- Temperature
- Respiratory rate
- Oxygen saturation
- Cephalic Centre Code
- Vapour ventilation
- Full clinical examination

Step 4. Investigations

- Electrocardiogram
- HbA1c
- FBC
- U&Es
- SGOT
- SBP/DBP
- Plasma electrolytes
- Blood glucose
- C-reactive protein
- Microalbumin
- Thyroid function tests
- Chest X-ray
- Urinary tract infection screen
- Full blood picture

Step 5. Outline monitoring regime

- Hourly capillary blood glucose
- Pulse and blood pressure every hour
- Ventricular fibrillation and pulse oximetry after 20 minutes
- 4-hourly and hourly thereafter
- Arterial and urine output
- Continuous pulse oximetry (if indicated)
- Continuous cardiac monitoring (if indicated)

Step 6. Look for precipitating causes and treat accordingly

Start broad-spectrum antibiotics. Infection is expected.

Modified from Management of DKA in Adults, NHS Trafford Diabetes, January 2012

Fluid And Potassium Replacement

<table>
<thead>
<tr>
<th>Initial Fluid &amp; Potassium Replacement</th>
<th>Potassium replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Restoration of circulating volume is a priority</strong></td>
<td><strong>Potassium level</strong></td>
</tr>
<tr>
<td><strong>Sympathetic</strong> BP (BP) 160/60 mmHg</td>
<td><strong>Potassium replacement 28 ml in 15 minutes</strong></td>
</tr>
<tr>
<td>Likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.</td>
<td><strong>3.5-4.5</strong></td>
</tr>
<tr>
<td><strong>Give 150 ml of 0.9% saline solution over 10-15 minutes. If BP remains 160/60 mmHg, repeat.</strong></td>
<td><strong>40 mmol/L (0.9 g/KG)</strong></td>
</tr>
<tr>
<td><strong>Maintain patients between 100-120 mmHg.</strong></td>
<td><strong>&gt;3.5</strong></td>
</tr>
<tr>
<td><strong>Consider adding 0.9% saline solution to give 1500 ml of 0.9% saline over the next 60 minutes.</strong></td>
<td><strong>Add additional potassium as required.</strong></td>
</tr>
<tr>
<td><strong>Addition of potassium is likely to be required in the second litre of fluid, especially if baseline potassium &lt;5 mmol/L and to maintain potassium between 4.5 mmol/L.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic</strong> BP admission 285 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Give 1000 ml of 0.9% saline for the first 60 minutes</strong></td>
<td></td>
</tr>
</tbody>
</table>

Caution: If potassium replacement is not seen, increase rate of fluid replacement.

Intensive Insulin Infusion The use of intensive insulin infusion is not included in current acute care guidelines.

- Start it at 0.1 U/kg/hour
- Titrate up to 0.3 U/kg/hour
- Aim for capillary blood glucose 10–14 mmol/L
- Aim for body weight 15–20% of goal
- More cautious fluid replacement in young people aged under 10 years, elderly, pregnant, febrile, or renal failure.
- Consider HCO3 and central line.

2-6th Hour

2nd-6th Hour

- Rate of fluid resuscitation of at least 8-10 ml/kg/hr, or
- Intravenous insulin (0.25 U/kg/hour, or
- Blood glucose fall 3 mmol/L/hour
- Maintain stable potassium in normal range
- Avoid hypoglycaemia

Step 7. Monitor patient, movement and signs

- Hourly blood glucose (finger blood glucose 6 mmol/L)
- 4-hourly blood pressure, no heart failure
- Venous blood gas for pH, bicarbonate and potassium at 8 hourly
- Data collected for at least 4-hourly, depending on the severity of illness
- If potassium is stable normal range, reassess potassium replacement and check 1 hour hourly depending on the severity of illness

Step 8. Continue fluid replacement via infusion pump as follows

- 1920 ml of 0.9% saline with potassium chloride over next 2 hours
- 1920 ml of 0.9% saline with potassium chloride over next 4 hours
- 1920 ml of 0.9% saline with potassium chloride over next 4 hours
- 1920 ml of 0.9% saline with potassium chloride over next 4 hours

- Stick to 70 kg maximum at 12.5 mmol/L and reduce insulin infusion rate to 0.25 U/kg/hour
- Switch to 50 kg maximum at 25 mmol/L, with no change in insulin infusion rate.

More cautious fluid replacement in young people aged under 10 years, elderly, pregnant, febrile, or renal failure.
- Consider HCO3 and central line.

Step 9. Assess response to treatment

- Start insulin pump, titrate insulin
- Blood glucose not falling for at least 0.5 mmol/L/hr
- Ventricular fibrillation not falling for at least 1 mmol/L/hr
- Plasma glucose not falling by at least 3 mmol/L/hr
- Venous bicarbonate not rising by at least 3 mmol/L/hr
- Venous bicarbonate >10 mmol/L, serum pH >7.5 and/or venous bicarbonate >10 mmol/L

- If potassium and glucose are not being as expected always check the insulin infusion pump is working and documented that the correct insulin infusion volume is present.

Step 10. If equipped to work for response to treatment is adequate, increase insulin infusion rate by 1 ml/hour every hour until

Additional measures

- Adjusted fluid balance chart, minimum urine output 0.5 ml/kg/hour
- Consider oral hydration in hospitalisation of 24 hours
- Reassess skin with sensory protection if pain is abnormally uncomfortable
- Measure ambulatory blood pressure and repeat CVP if oxygen saturation less than 90%
- More cautious fluid replacement and venous bicarbonate weight target
- Consider ECG monitoring if potassium abnormal or concern about cardiac arrhythmias.
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 prebreakfast, pre-lunch and pre-evening meal.
E.g. Short-acting insulin 7u tid & 20 units bedtime

Slide 10

What is the next step of management?

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

Slide 11

Example

An 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
management of diabetic emergencies 2
**Case Study**

A 43-year-old gentleman with a long history of type 2 diabetes (> 6 years), dyslipidemia and hypertension presented to the emergency department with a 6-day history of weakness, fever, nausea, vomiting and a painful left foot with foul smelling pus discharge from ulcer on the sole.

He was on glitazone and metformin since diagnosis. Mixtard 30 units bd was started 1 year ago because of poor glycaemic control.

Stopped injecting insulin for 1 week ago – poor appetite precipitated hypoglycaemia.

**Examination**

Temperature 38.9°C
BP 96/60 mmHg, Pulse 136 beats/minute, low volume
Respiration 36 breaths/minute, deep sighing breathing

Drowsy but arousable.
Tongue coated, dry mucosa and decrease skin turgor

Lungs clear; Heart sounds normal.
The abdominal exam - mild epigastric tenderness to deep palpation; no rebound tenderness or guarding.
Left foot suppurative ulcer with adjacent cellulitis extending to the knee.

Capillary blood glucose: 28 mmol/L

**Laboratory Results**

Urinalysis:
- Glucose 4+, ketones 3+, nitrite and leucocyte negative

Venous blood gas:
- pH of 7.06, pCO₂ 17 mmHg, bicarbonate 5.6 mmol/L

Blood glucose: 30 mmol/L

Blood lactate: 3.2 mmol/L (0.5 – 1.0 mmol/L)

Renal profile:
- Urea 12 mmol/L, sodium 142 mmol/L, potassium 5.6 mmol/L,
  chloride of 112 mmol/L, creatinine 136 µmol/L

FBC:
- Leucocyte 23 x 10⁹/L with predominant neutrophils, haematocrit 55%
**Imaging**

Chest X-ray: unremarkable

X-ray left foot:
- Diabetic foot with osteomyelitic changes of 1-3 metatarsals.

**More tests?**

- **Serum osmolality**
  - Formula: \( (0.5 \times \text{serum} + (\text{Na}^- + \text{K}^+ + \text{Cl}^- + \text{HCO}_3^-)) \times 1000 \)
  - Laboratory measured value: 326 mmol/L (Normal range 275-300 mmol/L)

- **Anion gap**
  - Formula: \( (\text{Na}^- + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-) \)
  - Result: 29.4 mmol/L (Normal range 5-15 mmol/L)

- **Others**
  - Septic workup
  - Pos: for culture and sensitivity
  - Blood cultures
  - ECO

**What is the diagnosis?**

- **This patient**
  - Blood glucose 30 mmol/L
  - Urine ketones 3+
  - Bicarbonate 5.6 mmol/L

- **Criteria for diabetic ketoacidosis**
  - Capillary blood glucose >11 mmol/L
  - Capillary ketones >3 mmol/L or urine ketones 2+
  - Venous pH <7.3 and/or bicarbonate <15 mmol/L

- **Diagnosis**
  - Diabetic ketoacidosis
SLIDE 7

What are the precipitating factors?

**Precipitating factors**
- Infection
- Missed insulin therapy
- Acute coronary syndrome
- CVA
- Surgery

**This patient**
- Infection of left foot
- Missed insulin therapy

SLIDE 8

What happen if treatment is delayed?

- High mortality rate:
  - Overall mortality is <1%
  - Mortality rate >5% in the elderly

SLIDE 9

**Prognosis**

- Excellent with prompt treatment
- High-dependency unit (HDU) care
management of diabetic emergencies 2
Hyperglycaemic Hyperosmolar State (HHS)

- Prompt diagnosis is important.
- Intensive management in high-dependency units or equivalent level of care.
- Common presentation in the young adults and elderly with multiple comorbidities.
- Higher mortality than DKA.

Hyperglycaemic Hyperosmolar State (HHS)

- Common: vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis.
- Uncommon: seizures, cerebral oedema and osmotic demyelination syndrome.
- Rapid changes in osmolality during treatment may also be the precipitant of osmotic demyelination syndrome.
- Progresses over many days → dehydration and metabolic disturbances are more extreme

Diagnostic Criteria of HHS

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

- There is **no significant hyperketaonemia** (<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
  - Significant electrolyte disturbances,
  - Hyperosmolality (>330 mosmol/kg),
  - Sudden drop in osmolality,
  - Severe dehydration,
  - Infection and sepsis,
  - Hypoglycaemia during treatment
  - Renal failure.

Dehydration in HHS

- 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.

Precipitating Factors For HHS

a) Infections and sepsis
b) Thrombotic stroke
c) Intracranial haemorrhage
d) Silent myocardial infarction
e) Pulmonary embolism
Management

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

What is the immediate management?

- **Hydration:** Intravenous (IV) 0.9% saline solution.

- Monitor serum osmolality regularly - prevent harmful rapid changes in osmolality.

- The rate of rehydration - assessing the combination of initial severity and any pre-existing comorbidities. Rapid rehydration - heart failure. Insufficient rehydration - 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.
What is the immediate management?

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

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

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

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

What is the immediate management?

- 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.
Case Study

management of diabetic emergencies 2
Case study

A 71-year-old obese lady with a 12-year history of T2DM.

Family members found patient confused after a fall at home. Associated with poor appetite urinary incontinence.

On metformin and gliclazide – since diagnosis, with inadequate diabetic control. Refused insulin therapy.

No self-monitoring of blood sugar levels at home.

Last A1c was 11.2% ~ 1.5 years ago.

Family members observed urinary and fecal incontinence.

Physical examination

BP 84/52 mmHg, Pulse rate 126 beats/minute
Temperature 38.6°C, Respiratory rate 24 breaths/minute
Peripheral oxygen saturation 100%

Dextrostix: H1

Drowsy, dysphasic, unable to swallow
Oral mucosa was dry and skin turgor diminished
Lungs decrease air entry right lower zone with coarse crepitations, no raised jugular venous pulse
Right sided hemiparesis
Examination of the abdomen - unremarkable.

Investigation results

Serum glucose 59.8 mmol/L

Renal profile
• Urea 14.6 mmol/L, sodium 154 mmol/L, potassium 5.4 mmol/L, chloride 110 mmol/L, creatinine 178 μmol/L

Arterial blood gases with bicarbonate 20 mmol/L

Urine FEME
• Cloudy, ketone 1+, nitrites and leucocytes present

Full blood count
• WBC 19 X 10⁹/L (80% polymorphonucleurs), hematocrit and platelet counts were normal

C-reactive protein: 134 mg/L (normal < 5)
ESR 85 mm/1st hour
Investigation results

ECG
- Sinus tachycardia, no ischaemic changes or right ventricular strain pattern

CXR:
- Consolidation right lower zone

More tests?

Serum osmolality
- Formula: \(2 \times \text{osm} + [\text{Na}^+] - ([\text{Na}^+] / 2)\) (where osm is osmolality, Na is sodium)
- Normal range: 275-295 mosmol/kg

Anion gap
- \([\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])\)
- Normal range: 8-16 mmol/L

Others

Septic workup
- Urea for culture and sensitivity

Blood cultures

Stroke workup
- including transfusion/10 and CT scan

What is the diagnosis?

This patient
- Dehydration - tachypnoea, tepid, dry mucous and eliminated skin
- Blurred vision due to retinopathy
- Urinary retention/viagra
- Fluoroscopic 20 ml/min - low andino

Criteria for Hyperglycaemic Hyperosmolar State
- Hyperosmolality - dehydration
- Nephrophagia/glucometria - 0.3 meq/L
- pH < 7.3, bicarbonate < 16 meq/L
- Glucose in blood ranges 0-11 mmol/L
- Brain osmolality > 320 mOsm/kg

Diagnosis
- Hyperglycaemic Hyperosmolar State
What are the precipitating factors?

- Infection and sepsis
- Thrombotic stroke
- Intracranial haemorrhage
- Silent myocardial infarction
- Pulmonary infarction

This patient
- Stroke

What happen if treatment is delayed or not properly carried out?

- Vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis are common.
- Seizures, cerebral oedema and osmotic demyelination - uncommon
- Rapid changes in osmolality - precipitant of osmotic demyelination syndrome.
- Mortality higher than DKA

What are the management goals?

Gradually and safely:
1. Normalise the osmolality
2. Replace fluid and electrolyte losses
3. Normalise blood glucose
4. Prevention of complications

Treat the underlying cause: stroke management and aspiration pneumonia

Care in high dependency ward
What is the immediate management?

- Hydration
- Insulin
- Electrolytes balance

Hydration

- Intravenous (IV) 0.9% saline solution.
- Monitor serum osmolality regularly - prevent harmful rapid changes in osmolality.
- The rate of rehydration - assessing the combination of initial severity and any pre-existing comorbidities. Rapid rehydration - heart failure. Insufficient rehydration - 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.

Insulin

- Low dose IV insulin (0.05 units/kg/hr) 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.
Electrolytes

- 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.
management of chronic complications 1
Overview

Microvascular Complications:
- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular Complications:
- Coronary Heart Disease
- Cerebrovascular Disease

Combination of Micro- and Macrovascular complications:
- Diabetic Foot
- Erectile Dysfunction

Diabetic Retinopathy (DR): Introduction

- Prevalence of DR is 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.

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

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

Retinopathy: Screening

- Initial assessment should be conducted at time of diagnosis of T2DM and annually thereafter.

- Pregnant women with T2DM should have retinal examination during each trimester.

- DR screening is not required for GDM. However, if GDM is diagnosed in the first trimester of pregnancy, screening should be as per pre-existing DM.
**Eye Examination**

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

---

**DIABETIC RETINOPATHY**

- Hemorrhages
- Abnormal growth of blood vessels
- Aneurysm
- "Cotton wool" spots
- Hard exudates

---

**Non-proliferative diabetic retinopathy**

- Aneurysm
- Hemorrhage
- Hard exudate

**Proliferative diabetic retinopathy**

- Growth of abnormal blood vessels
VEGF plays an important role in the development of DME. Anti-VEGF has proven 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.

Two drugs approved US FDA and EMA – Ranibizumab and Aflibercept.
Retinopathy: Treatment

- Mainstay of current treatment involves risk factor modification by controlling:
  - tight blood glucose
  - blood pressure
  - serum lipids

- Other modalities of risk factor modification include:
  - diet,
  - Exercise
  - stop smoking.

Retinopathy: Treatment

- 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.

- Laser photocoagulation remains the standard practice for treating DR.

- # Intra-ocular anti vascular endothelial growth factor (anti-VEGF) is a novel therapy for DR.

- Stages of DR which require treatment includes severe Non-Proliferative DR, Proliferative DR, Advance Eye Disease and Diabetic Macular Oedema (DME).

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

Nephropathy: Screening

- A more sensitive and specific test called the Urine Albumin Creatinine Ratio (ACR) may be performed in those with negative microalbuminuria.
- ACR - 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.

Nephropathy: Screening

- 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.
- Measurement of GFR could easily be performed by using the MDRD formula which can be accessed at http://www.mdrd.com.

Recommendations for Screening Nephropathy

1. Screening for proteinuria should be performed at diagnosis and annually with conventional dipstick on an early morning urine specimen. [Grade C]
2. If urine dipstick for proteinuria is negative, screening for microalbuminuria should be [Grade C]
3. If microalbuminuria is detected, confirmation should be made with further tests 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 the proteinuria, serum creatinine level should be measured annually to determine GFR. [Grade C]
Proteinuria is an independent predictor for nephropathy progression. The magnitude of proteinuria as measured by 24-hour urine collection has a linear relationship with progression of nephropathy and risk of CV events.

**Nephropathy: Management**

- BP and glycaemic control crucial in preventing or retarding progression of diabetic nephropathy.
- Dose adjustment of anti-diabetic agent may be necessary.
- 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. In a proportion of patients, microalbuminuria may be normalised by ACEIs or ARBs even if the BP is optimally controlled with close monitoring of potassium level.
- Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate.

**Nephropathy: Management**

- Decrease protein intake to 0.8 g/kg body weight per day in individuals with diabetes at stage III and IV 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.
- ACEIs or ARBs should be initiated unless contraindicated to slow progression of diabetic nephropathy.
- Other measures:
  - Lipid control
  - Stop smoking
  - Weight reduction
  - Moderate protein and salt restriction
### SLIDE 20

**Stages of CKD**

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

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

*Adapted from National Kidney Foundation, KDQI Clinical Practice Guidelines for Chronic Kidney Disease 27th Level III.

### SLIDE 21

**Staging of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Previous NKF CKD stage</th>
<th>Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category</th>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A1</td>
<td>Normal or high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2</td>
<td>Moderately increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3</td>
<td>Severely increased</td>
</tr>
<tr>
<td>1 G1</td>
<td>Normal or high</td>
<td>1 if CKD</td>
<td>1</td>
</tr>
<tr>
<td>2 G2</td>
<td>Mildly decreased</td>
<td>1 if CKD</td>
<td>1</td>
</tr>
<tr>
<td>3 G3a</td>
<td>Mildly to moderately decreased</td>
<td>1 if CKD</td>
<td>1</td>
</tr>
<tr>
<td>4 G4</td>
<td>Severely decreased</td>
<td>1 if CKD</td>
<td>1</td>
</tr>
<tr>
<td>5 G5</td>
<td>Kidney failure</td>
<td>1 if CKD</td>
<td>1</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.

### SLIDE 22

**Referral to nephrologist**

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

*Adapted from Malaysian Clinical Practice Guidelines for the Chronic Kidney Disease in Adults.
**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]

---

**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**

- 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.
- DPN may be asymptomatic in a large proportion of cases (up to 50%) and requires clinical examination to document/unveil its existence. It causes or contributes to significant morbidity and mortality.
- Studies from tertiary centres showed that prevalence of DPN ranged between 50 to 80%.
Neuropathy: Screening

- Neuropathy should be assessed with a 10-g monofilament; and one other modality:
  a) Pin prick
  b) Vibration sense using 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%.

- These bedside tests should be performed at least annually.

Neuropathy: Treatment

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

- No pharmacology 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 second line therapy.

- Topical treatment (e.g. capsaicin cream, lidocaine 5% patch) may be added to systemic treatment at any time.

Diabetic Autonomic Neuropathy

- DAN results in significant morbidity and may lead to mortality in some patients with diabetes. In particularly CAN, is an independent risk factor for cardiovascular mortality.

- Clinical manifestations of DAN include:
  - resting tachycardia,
  - exercise intolerance,
  - orthostatic hypotension,
  - gastroparesis, constipation,
  - erectile dysfunction,
  - sudomotor (sweat glands) dysfunction
  - impaired neurovascular function
  - autonomic failure in response to hypoglycaemia.
DAN: Treatment

- Intensive control of cardiovascular modifiable risk been shown to reduce the progression and development of CAN among patients with T2DM.

- Avoid drugs causing orthostatic hypotension. Midodrine has been approved as medical therapy for orthostatic hypotension.

- Prokinetic agent such as erythromycin aids in relieving gastroparesis symptoms.

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

Recommendations: Neuropathy

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

- Mr AB is a 65-year-old man presents with complaints of fatigue and increased frequency of urination for the past 3 to 4 weeks.
- He has been feeling tired even with mild exertion and feels like resting most of the time.
- He has also been seeing occasional dark spots floating in his visual field (floaters) for the past 3 to 4 weeks, although these do not really trouble him much.

Further questioning

- The patient had no complaints of associated fever, chest pain or tightness, change in appetite or weight, palpitations, oedema, excessive sweating, burning pain during micturition or loss of consciousness.
- He has a family history of diabetes in paternal grandfather and father.

On Examination...

- Weight 84 kg
- Height 171 cm
- WC 96 cm
- BP 150/100 mmHg
- Both eyes: capillary microaneurysms, dot and blot retinal haemorrhages and cotton-wool spots (soft exudates)
- Both feet: reduced sensation
Lab Investigations

- FBS: 10mmol/L
- PPBG: 13 mmol/L
- HbA1c: 7.8%
- Urinalysis: Protein 2+
- Tchol : 5.8 mmol/L
- HDL-C: 0.8 mmol/L
- LDL-C: 3.2 mmol/L
- TG : 2.1 mmol/L

Current Treatment

- He had been on metformin 500mg BID for the past 5 years, which was then uptitrated to 1000 mg BID 6 months ago.

Question

- What are his problems?
  - Long standing poorly controlled diabetes
  - High blood pressure – to confirm whether has Hypertension
  - Dyslipidaemia (LDL 3.2, TC 5.8, TG 2.1)
  - Presence of diabetes complications (retinopathy, peripheral neuropathy)
**Question:**

- What are the risk factors for retinopathy?
  - Duration of DM
    - At diagnosis: 60% T2DM
    - By 20 years: 100% (AR)
  - Poor control of DM
  - Obesity
  - Other co-morbidities - HPT, hyperlipidemia, anaemia
  - Smoking
  - Pregnancy
  - Nephropathy

**Question**

- Why need to have Diabetic eye Screening?

<table>
<thead>
<tr>
<th>Why need to have Diabetic eye Screening?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Magnitude of disease</strong></td>
</tr>
<tr>
<td><strong>Seriousness</strong></td>
</tr>
<tr>
<td><strong>Early detection</strong></td>
</tr>
<tr>
<td><strong>Screening tests</strong></td>
</tr>
<tr>
<td><strong>Early treatment</strong></td>
</tr>
</tbody>
</table>
Question?

- When do you screen for retinopathy? (schedule for examination)

---

**CPG Schedule for Fundus Examination**

<table>
<thead>
<tr>
<th>Time of onset of DM</th>
<th>Recommended time of 1st exam</th>
<th>Routine minimum FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 years of age (Type 1 DM)</td>
<td>5 years after onset</td>
<td>Yearly</td>
</tr>
<tr>
<td>Age 30 and older (Type 2)</td>
<td>At time of diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Before pregnancy (DM pt who plan for childbirth)</td>
<td>Before or soon after conception</td>
<td>3 monthly</td>
</tr>
</tbody>
</table>

-Audit NDR 2012 – 44% diabetics had eye checked

---

Question

- How do you perform eye screening for retinopathy?
**Slide 13**

**Fundus assessment**
- Direct ophthalmoscopy
- Slit-lamp biomicroscopy with contact lens
- Binocular indirect ophthalmoscopy
- Fundus photography

**Slide 14**

**Question**
- When do you refer your patient with Diabetes Retinopathy?
  1. Severe Non-Proliferative DR
  2. Any level of Diabetic Maculopathy
  3. Any Proliferative DR
  4. Unexplained visual loss
  5. If screening examination cannot be performed including ungradable fundus photo

**Slide 15**

**Question**
- How would you manage him?
  - Optimization of his hypoglycaemic agent – start on combination therapy. Discussed regarding insulin therapy if glycaemic target not achieved within 3-6 months
  - Check on monitoring on blood sugar
  - Initiate dyslipidaemia therapy
  - If confirmed nephropathy, target BP is < 135/75
  - Anti-platelet agent as patient have multiple risk factors
Question

• How would you manage him?
  – Refer to eye specialist
  – Advise on Foot care (as having neuropathy)
  – Review dietary practices and refer to see Dietitian
  – Weight reduction.
  – Physical activity
management of chronic complications 2
Coronary Heart Disease

- Diabetic patients are at increased risk of CHD. They may manifest as angina, myocardial infarction (MI), congestive cardiac failure (CCF) or sudden death.
- Most frequent cause of death in T2DM.
- Characterised by its early onset, extensive disease at the time of diagnosis, and higher morbidity and mortality after MI.

OASIS Study: Total Mortality

Cardiovascular mortality in relation to diabetes mellitus and a prior MI: A Danish Population Study of 3.3 Million People
**NCVD-ACS Registry**

<table>
<thead>
<tr>
<th>CV Risk factors</th>
<th>2006 (N=3382)</th>
<th>2007 (N=3680)</th>
<th>2008 (N=2839)</th>
<th>2009 (N=3594)</th>
<th>2010 (N=3461)</th>
<th>Total (N=16,896)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>33</td>
<td>33</td>
<td>31</td>
<td>35</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61</td>
<td>63</td>
<td>56</td>
<td>64</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>44</td>
<td>44</td>
<td>38</td>
<td>44</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Family History of premature CVD</td>
<td>12</td>
<td>13</td>
<td>9</td>
<td>9</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>MI history</td>
<td>16</td>
<td>18</td>
<td>13</td>
<td>26</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Documented CAD</td>
<td>15</td>
<td>18</td>
<td>14</td>
<td>20</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>New onset angina (CCS criteria)</td>
<td>45</td>
<td>53</td>
<td>48</td>
<td>68</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Chronic angina (past &gt;3 weeks ago)</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>33</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>BMI &gt; 23kg/m²</td>
<td>75</td>
<td>74</td>
<td>73</td>
<td>78</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

**Risk Factors:**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>3.50%</td>
</tr>
<tr>
<td>CRF</td>
<td>7.61%</td>
</tr>
<tr>
<td>BVS/LPD</td>
<td>82%</td>
</tr>
<tr>
<td>FAMILY HIST</td>
<td>3.70%</td>
</tr>
<tr>
<td>EX-SMOKER</td>
<td>3.06%</td>
</tr>
<tr>
<td>SMOKING</td>
<td>7.00%</td>
</tr>
<tr>
<td>HPT</td>
<td>7.00%</td>
</tr>
</tbody>
</table>

Overall outcomes for pts with ACS, Malaysia 2006

- elderly age group: 10% in-hospital mortality, 13% 30-day mortality
- Female patients: 8% in-hospital mortality, 10% 30-day mortality
- male patients: 6% in-hospital mortality, 8% 30-day mortality
- diabetes: 7% in-hospital mortality, 10% 30-day mortality
- without diabetes: 5% in-hospital mortality, 6% 30-day mortality
Screening

- Typical symptoms: referral to cardiologist.
- May have atypical/vague symptoms especially trigger by exertion.
- Asymptomatic: routine screening not recommended.
- On first and subsequent visit, CVD risk calculator such as Framingham Risk Score (FRS) or SCORE should be applied.
- Patient with other macrovascular complications should be screen for CHD.

ASA and diabetes: 2008 JPAD

<table>
<thead>
<tr>
<th>Clinical outcomes</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point*</td>
<td>0.80 (0.58–1.10)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fatal coronary or cerebrovascular events</td>
<td>0.10 (0.01–0.79)</td>
<td>0.0037</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.90 (0.57–1.41)</td>
<td>0.67</td>
</tr>
<tr>
<td>Atherosclerotic events* (among age &gt;65 y)</td>
<td>0.68 (0.46–0.99)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

*Composite of sudden death; death from coronary, cerebrovascular, or aortic causes; nonfatal MI, unstable angina, new exertional angina, nonfatal ischemic or hemorrhagic stroke; transient ischemic attack; or nonfatal aortic or peripheral vascular disease

ASA and diabetes: 2008 JPAD: Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin Group (n = 1282)</th>
<th>Nonaspirin Group (n = 1277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>65 ± 10</td>
<td>64 ± 10</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>706 (56)</td>
<td>681 (53)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>289 (23)</td>
<td>248 (19)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>24 ± 4</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>742 (59)</td>
<td>731 (57)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>680 (54)</td>
<td>669 (52)</td>
</tr>
<tr>
<td>Duration of diabetes (y), median (IQR)</td>
<td>7.3 (5.8–12.3)</td>
<td>8.7 (3.8–12.5)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)*</td>
<td>136 ± 15</td>
<td>134 ± 15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)*</td>
<td>77 ± 9</td>
<td>76 ± 9</td>
</tr>
</tbody>
</table>

*Mean ± SD.
**ASNA and diabetes: 2008**

**JPAD: Primary end point**

Primary End Point: Total Atherosclerotic Events According to the Treatment Groups

![Graph showing End Point: Total Atherosclerotic Events According to the Treatment Groups](image)

Ogawa H et al. JAMA 2008 (300) 18; 2134-2141

---

**ASNA and diabetes: 2008**

**JPAD: Primary end point if 65 years or older**

Total Atherosclerotic Events According to the Treatment Groups: Subgroup—Aged 65 Years or Older

![Graph showing Total Atherosclerotic Events According to the Treatment Groups: Subgroup—Aged 65 Years or Older](image)

Ogawa H et al. JAMA 2008 (300) 18; 2134-2141

---

**ASA for 1° Prevention in Diabetes**

Meta analysis of 6 studies (n = 10,117)

- No overall benefit for:
  - Major CV events
  - MI
  - Stroke
  - CV mortality
  - All-cause mortality

---

**Notes:**

- **JPAD:** Japanese Primary Prevention of Atherosclerosis Disease Study
- **PPAP:** Prevention of Progression of Arterial Disease and Early Assessment of Cardiovascular Risk Study
- **PHS:** Physicians Health Study
- **WHS:** Women’s Health Study

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

- The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study showed that daily low-dose aspirin failed to show a significant effect on broad composite cardiovascular disease endpoints.
- Fatal coronary or cerebrovascular events was significantly decreased in the aspirin group in those above the age of 65.
- Low dose aspirin (100 mg) in those aged 65 or older has been shown to reduce atherosclerotic events.

**Cerebrovascular Disease**

- Risk are increase twice of ischaemic stroke compared to those without diabetes.
- The risk of stroke is higher in women than in men.
- Dyslipidaemia, endothelial dysfunction and platelet or coagulation abnormalities are among the risk factors that promote the development of carotid atherosclerosis in diabetics.

**Diabetic Foot**

- Ulcerations and amputations are major causes of morbidity and mortality.
- Prevalence of lower limb amputation was 4.3%.
- Risk factors for foot ulcers:
  - Previous amputation
  - Past foot ulcer history
  - Peripheral neuropathy
  - Foot deformity
  - Peripheral vascular disease
  - Visual impairment
  - Diabetic nephropathy (especially patients on dialysis)
  - Poor glycaemic control
  - Cigarette smoking
Prevention of Foot Ulcers

- Starts with examination of the feet (shoes and socks removed) and identifying those at high risk of ulceration. Assess the peripheral neuropathy and peripheral pulses.
- 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.

Treatment

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

- Definition: Inability to achieve, maintain or sustain an erection firm enough for sexual intercourse.
- Prevalence of ED among diabetic men varies from 35% to 90%.
- Factors associated:
  - Advancing age, duration of diabetes, poor glycaemic control, presence of other diabetic complications, hypertension, hyperlipidaemia, sedentary lifestyle and smoking

Screening and Diagnosis

- All adult diabetic males should be asked about ED.
- Screened for any symptoms or signs of hypogonadism.
- Screening can be done using the 5-item version of the International Index of Erectile Function (IIEF) questionnaire.
### Slide 22

**Indeks Fungsi Seka Anterambangga (IFAS)**

Suatu sistem yang berfungsi untuk mengontrol sebaran kecepatan dan arah aliran pasokan. Sekarang ini metode pengukuran yang diminati untuk mengetahui tingkat kecepatan dan arah aliran pasokan. Metode pengukuran ini digunakan dalam berbagai bidang ilmu seperti geofisika, teknik, dan pengukuran aliran air.

- **Kegunaan sekala:** Analisis pengukuran, pembuatan informasi, pengujian, dan perilaku pasokan.
- **Pendekatan:** Metode pengukuran kecepatan aliran (IFAS) dan aliran pasokan (IFAS) serta analisis yang dilakukan secara keseluruhan pada unit analisis.
- **Pengukuran sekala:** Metode pengukuran kecepatan aliran (IFAS) dan aliran pasokan (IFAS) serta analisis yang dilakukan secara keseluruhan pada unit analisis.
- **Tanpa analisis:** Pemanfaatan aliran dan arah aliran yang diperlukan untuk pemanfaatan aliran dan arah aliran.

<table>
<thead>
<tr>
<th>Alat &amp; Metode Analisis</th>
<th>Kegunaan</th>
<th>Kualitas</th>
<th>Kuantitas</th>
<th>Tingkat</th>
<th>Sarat</th>
<th>Sisa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kegunaan Pasokan</td>
<td>Low</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total Kegunaan Pasokan</td>
<td>Medium</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total Kegunaan Pasokan</td>
<td>High</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total Kegunaan Pasokan</td>
<td>Very High</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Total Kegunaan Pasokan</td>
<td>Extreme</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

### Slide 23

**Treatment**

- Optimisation of glycaemic control, management of other comorbidities and lifestyle modifications.
- Psychosexual counseling for patient and partner is recommended.
- Avoid medications that may cause or worsen ED such as thiazides, beta-blockers, calcium channel blockers, methylidopa etc.
- Phosphodiesterase-5 (PDE-5) inhibitors should be offered as first-line therapy.
- Referral to a urologist may be necessary for those not responding.

### Slide 24

**Female Sexual Dysfunction**

- Occur in 24–75% in diabetic women.
- Age, duration of diabetes, poor glycaemic control, menopause, microvascular complications, and psychological factors are associated with FSD.
Screening and Diagnosis

Figure 6: Sexual Symptom Checklist for Women

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

* Diagnosis of FSD can be established by using the FSFI questionnaire that consists of 19 questions covering all domains of sexual dysfunction available at www.fsfquestionnaire.com. The validated Malay version is also available.

Treatment

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

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

- In postmenopausal women, tibolone has been associated with significant increases in sexual desire and arousal.

Mental Health Issues in Diabetes

- Symptoms to look for may include the prolonged period of moodiness with any or all of the following:
  - Appetite changes
  - Loss of interest in daily activities
  - Feeling of despair
  - Inappropriate sense of guilt
  - Sleep disturbance
  - Weight loss
  - Suicidal thoughts
Indications for referral to a mental health specialist may include:
- Depression with the possibility of self-harm
- Debilitating anxiety (alone or with depression)
- Indications of an eating disorder
- Cognitive functioning that significantly impairs judgment
Case Study

management of chronic complications 2
**Case 1**

Mrs NS is a 58-year-old university lecturer;

Medical History:
1. T2DM past 10 years
2. Hypertension past 8 years
3. Hyperlipidaemia past 10 years

Treatment:
1. Mixtard 36 units BID
2. Actrapid 12 units pre lunch
3. Metformin 850 mg BID
4. Ibersartan 150 mg daily
5. Atorvastatin 20 mg daily

Physical:
Wt 62 kg, BMI 23 kg/m², BP 135/82 mmHg, pulse 84/min

Lab results:
- A1c 6.4%
- FBG 5.8 mmol/l
- LDL 2.2 mmol/l
- HDL 1.1 mmol/l
- TG 1.3 mmol/l
- Normal renal function
- No proteinuria

---

**Slide 2**

She comes in for her routine clinic appointment; Quite happy with herself.

Still doing aerobics 1 hour 3 times a week.
She reduces her evening dose of mixtard to 24-28 units followed by a light snack during her aerobic nights. After the aerobics she will have a light supper.

Her last hypo was almost 2 years ago when she forgotten to take her snack. It hasn't occurred since.

Taking care of her diet and does gardening over the weekends.

She is asymptomatic and has a good effort tolerance.
She takes Evening Primrose Oil for the occasional hot flushes that she gets at night

Lab results:
- A1c 6.4%
- FBG 5.8 mmol/l
- LDL 2.2 mmol/l
- HDL 1.1 mmol/l
- TG 1.3 mmol/l
- Normal renal function
- No proteinuria

---

**Slide 3**

Subsequent Clinic Visit 6 months later;

She related that she had chest pain during her daughter's birthday and was rushed to the nearest hospital. The attending cardiologist made a diagnosis of (unstable) angina and proceeded with coronary angiogram which showed a single vessel disease in the LAD. A drug eluting stent was placed.

The cardiologist informed her that he had to reduced her insulin levels now that she has IHD as strict glycaemic control is associated with increased mortality (ACCORD Study).

Her current medications:
- Basal insulin 24 units at bedtime
- Gliclazide 60 mg daily
- Metformin 850 mg BID
- Aspirin, Clopidogrel
- Bisoprolol, Ibesartan & Atorvastatin 40 mg

Lab results:
- A1c 8.4%
- FBG 6.8 mmol/l
- LDL 1.8 mmol/l
- HDL 1.2 mmol/l
- TG 1.8 mmol/l
- Normal renal function
- No proteinuria
Lab results:
- A1c 8.4%
- FBG 6.8 mmol/l
- LDL 1.8 mmol/l
- HDL 1.2 mmol/l
- TG 1.8 mmol/l
- Normal renal function
- No proteinuria

1. How would you have modified her diabetes treatment?

2. What will you do now?

3. Do you agree with the application of the ACCORD’s data?
**Slide 7**

**ACCORD Treatment Effect on Primary Outcome**

![Graph showing the effect of standard and intensive therapy on patients with events over time.](image)


**Slide 8**

**Cardiovascular Deaths in ACCORD**

![Graph showing the incidence of mortality in ACCORD.](image)

Sudden death accounted for nearly two thirds of cardiovascular deaths: 86/135 with intensive therapy and 67/94 with standard therapy.

**Slide 9**

**Mortality Associated with Severe Hypoglycemia**

![Graph showing mortality associated with severe hypoglycemia in ACCORD.](image)

### ACCORD: Hazard Ratios for Primary Outcome by Subgroup

<table>
<thead>
<tr>
<th>Protocol Defined Subgroups</th>
<th>N</th>
<th>Events</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10251</td>
<td>723</td>
<td></td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>6643</td>
<td>330</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>3608</td>
<td>393</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>3952</td>
<td>212</td>
<td>0.74</td>
</tr>
<tr>
<td>Men</td>
<td>6299</td>
<td>511</td>
<td></td>
</tr>
<tr>
<td>Baseline Age&lt;65</td>
<td>6779</td>
<td>383</td>
<td>0.65</td>
</tr>
<tr>
<td>Baseline Age≥65</td>
<td>3472</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>Baseline A1C≤8.0</td>
<td>4868</td>
<td>284</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline A1C&gt;8.0</td>
<td>5360</td>
<td>438</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>3647</td>
<td>222</td>
<td>0.29</td>
</tr>
<tr>
<td>White</td>
<td>6604</td>
<td>501</td>
<td></td>
</tr>
</tbody>
</table>


### Background: Mortality By Severe Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Never Experienced a Hypoglycemic Event</th>
<th>Experienced Hypoglycemic Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mortality Rates</td>
<td>1.2% / year (257 Deaths)</td>
<td>3.3% / year (223 Deaths)</td>
</tr>
<tr>
<td>Intensive Glycemia</td>
<td>1.3% / year (223 Deaths)</td>
<td>2.8% / year (34 Deaths)</td>
</tr>
<tr>
<td>Standard Glycemia</td>
<td>1.1% / year (186 Deaths)</td>
<td>4.9% / year (17 Deaths)</td>
</tr>
</tbody>
</table>

Again, mortality is higher among participants who had experienced a Severe Hypoglycemic Event, regardless of treatment strategy.

### Mortality By Treatment Group and Severe Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Never Experienced a Hypoglycemic Event</th>
<th>Experienced Hypoglycemic Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Glycemia</td>
<td>1.4% / year (283 Deaths)</td>
<td>1.3% / year (226 Deaths)</td>
<td>2.8% / year (24 Deaths)</td>
</tr>
<tr>
<td>Standard Glycemia</td>
<td>1.1% / year (283 Deaths)</td>
<td>1.1% / year (186 Deaths)</td>
<td>4.9% / year (17 Deaths)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>1.22 (1.01, 1.46)</td>
<td>1.24 (1.02, 1.50)</td>
<td>0.54 (0.30, 0.96)</td>
</tr>
</tbody>
</table>

Mortality Higher in **Intensive Group**
Mortality Higher in **Standard Group**

*Interaction P < 0.01*
Lab results:
- A1c 8.4%
- FBG 6.8 mmol/l
- LDL 1.8 mmol/l
- HDL 1.2 mmol/l
- TG 1.8 mmol/l
- Normal renal function
- No proteinuria

1. How would you have modified her diabetes treatment?
2. What will you do now?
3. Do you agree with the application of the ACCORD’s data?
4. What will be your final decision on her diabetes treatment?

Lab results:
- A1c 9.4%
- FBG 8.8 mmol/l
- LDL 2.5 mmol/l
- HDL 0.9 mmol/l
- TG 2.3 mmol/l
- Normal renal function
- No proteinuria

Case 2

A 54-year-old lawyer comes to see you a day after the death of his brother from myocardial infarction.

The patient has the following medical conditions:
1. T2DM past 4 years
2. Hyperlipidaemia past 10 years
3. Hypertension past 10 years.

His treatment consists of:
1. Gliclazide MR120 mg OD
2. Metformin XR 750 mg BID
3. Rosuvastatin 10 mg OD
4. Ramipril 10 mg OD
5. Amlodipine 10 mg OD

Vital Stats
- Wt: 84 kg
- BMI: 34 kg/m²
- BP 135/85 pulse 88/min

He asks if he warrants a referral to the cardiologist perhaps for coronary angiogram seeing the fate of his brother.

1. What will you do next?
He asks if he warrants a referral to the cardiologist perhaps for coronary angiogram seeing the fate of his brother.

1. What will you do next?
   A. Put him on a stop smoking programme
   B. Optimise his BP
   C. Encourage him to exercise to raise his HDL
   D. Intensify his DM treatment

E. Choices:
   1. Single anti-diabetic agent
   2. Two anti-diabetic agents
   3. Basal insulin
   4. GLP-1 RA
   F. Watch for his weight

Lab results:
- A1c: 9.4%
- FBG: 8.8 mmol/l
- LDL: 2.5 mmol/l
- HDL: 0.9 mmol/l
- TG: 2.3 mmol/l
- Normal renal function
- No proteinuria
3.7.3 Algorithm E: Suggested Treatment Approach for Specific Patient Profiles

Answers the question: What would you give yourself if you were a patient?

Recommendations based on 5 priorities:
1. Safety
2. Convenience to aid compliance
3. CVR: Global Risk Reduction (eg obesity)
4. Glycaemic Efficacy
5. Cost

Note:
- Patients who are well-controlled on their existing
- Bariatric surgery may be considered in patients

Legend:
- Consider first line
- Consider second line
- Consider third line
- Consider fourth line
- Consider fifth line
- Consider sixth line

2nd Gen SU or DPP-4 i
- 2nd generation sulphonylurea
- Dipeptidyl peptidase-4 inhibitor (DPP-4 i)
- GLP-1 RA
- GLP-1 receptor agonist
- GLP-1 RA
- GLP-1 receptor agonist
- Insulin
- Insulin
- SGLT2i
- Sodium-glucose cotransporter-2 inhibitor (SGLT2i)
- Metformin
- Metformin
- Metformin
- Metformin
diabetes in special populations 1
Diabetes in Pregnancy

- Gestational diabetes mellitus
- Pre-existing Type 1 and Type 2 DM

Maternal complications in diabetic pregnancy

- Hypoglycemia, ketoacidosis
- Pregnancy-induced hypertension
- Pyelonephritis, other infections
- Polyhydramnios
- Preterm labor
- Worsening of chronic complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Cardiac disease

Complications for infants of mothers with DM

- Congenital malformations
- Macrosomia
- Birth injury
- Asphyxia
- Respiratory Distress Syndrome
- Perinatal mortality
- Metabolic abnormalities
  - Hypoglycaemia
  - Hypokalemia
  - Hypocalcemia
  - Hyperbilirubinemia
  - Erythrosis
**GDM**

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

**GDM- risk in the subsequent pregnancies**

<table>
<thead>
<tr>
<th>Region/descriptor</th>
<th>GDM count</th>
<th>GDM %</th>
<th>Age at index pregnancy (years)</th>
<th>Time between pregnancy (months)</th>
<th>Risk of GDM (women %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>692</td>
<td>38</td>
<td>28</td>
<td>2.5 years</td>
<td>45</td>
</tr>
<tr>
<td>South</td>
<td>662</td>
<td>28</td>
<td>28</td>
<td>2.5 years</td>
<td>45</td>
</tr>
<tr>
<td>East</td>
<td>659</td>
<td>30</td>
<td>28</td>
<td>2.5 years</td>
<td>45</td>
</tr>
<tr>
<td>West</td>
<td>648</td>
<td>32</td>
<td>28</td>
<td>2.5 years</td>
<td>45</td>
</tr>
</tbody>
</table>

The risk of GDM in subsequent pregnancies ranges from 30-84%.

**Gestational Diabetes Mellitus: Clinical Predictors and Long-Term Risk of Developing Type 2 Diabetes**

A retrospective cohort study using survival analysis

- **CUMULATIVE PROBABILITY**
  - DEV TYPE 2 DM
  - 1 YEAR – 1.7%
  - 2 YEARS-2.6 %
  - 5 YEARS – 8.1%
  - 10 YEARS-17.3%
  - 15 YEARS- 25.8%

There is also increased risk of type 2 DM where the cumulative risk of developing Type 2 DM is 25.8% in 15 years.
HAPO is a study where a 75-g oral glucose tolerance test (OGTT) was performed on a heterogeneous, multinational, ethnically diverse cohort of 23,316 pregnant women at 24–32 weeks’ gestation. OGTT done at 0 min, 1 hr and 2 hours. The result showed continuous association of maternal blood glucose levels below those diagnostic of diabetes with birth weight and cord blood serum C peptide levels. This further leads to the development of IADPSG guideline where diagnosis of gestational diabetes is made based on 1 abnormal test: FBS > 5.1 mmol/l, 1 hr > 10 mmol/l, 2 hr > 8.5 mmol/l.
Preferably universal screening is advised as the prevalence of Type 2 DM is increasing in Malaysia. However, due to limited resources, the high risk groups should be identified and the screening should be done at booking. If the result is normal, then a repeat OGTT should be done 4-6 weeks later.

Screening - risk factors

- BMI >27 kg/m²
- Previous macrosomic baby weighing ≥4 kg
- Previous gestational diabetes mellitus
- First-degree relative with diabetes
- History of unexplained intrauterine death
- History of congenital anomalies
- Glycosuria at the first or any prenatal visit
- Current obstetric problems (essential hypertension, pregnancy-induced hypertension, polyhydramnios and current use of steroids)
The pregnancy has to be planned only when the woman has good glycaemic control, has had appropriate assessment and management of comorbidities, and has discontinued potentially unsafe medications during pregnancy.
The concern of insulin analogues is the high affinity of IGF1 receptor thus increasing the risk of big babies and worsening retinopathy. However the use of basal insulin analogues (insulin detemir and glargine) during pregnancy has not been associated with adverse maternal and fetal outcome.
Pre-conception Management

- Screen for diabetic retinopathy
- Screen for diabetic nephropathy prior to pregnancy.
- Satisfactory BP control of <130/80 mmHg before pregnancy is necessary.
- 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.

SMBG during Pregnancy

- Monitoring should be done at the following times (spread out over a few days):
  - Fasting (following an 8-hour of overnight fast) and before each meal.
  - 1 or 2 hours after the start of each meal (post-prandial).
  - Bedtime and during the night if indicated.
  - Frequent monitoring in those with poorly controlled diabetes
  - BSP – done at the clinic probably is not a true reflection of the blood glucose control

Glycaemic targets in pregnancy

<table>
<thead>
<tr>
<th>Timing</th>
<th>Glucose Level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting or premeal</td>
<td>≤ 5.3</td>
</tr>
<tr>
<td>1 hour post prandial</td>
<td>≤ 7.8</td>
</tr>
<tr>
<td>2 hour post prandial</td>
<td>≤ 6.7</td>
</tr>
</tbody>
</table>
Nutrition and Weight Management

- Important to receive medical nutrition therapy defined as a carbohydrate controlled meal plan that promotes:
  - Adequate nutrition with appropriate weight gain
  - Normoglycaemia, and
  - Absence of ketosis.

Weight Management

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

- Normal pre-pregnancy weight, caloric prescription should be as per normal pregnancy (35 kcal/kg body weight)

- Overweight/obese women, moderate caloric restriction (25 kcal/kg body weight) is advocated without inhibiting foetal growth, birth weight or inducing ketosis.

- Carbohydrate intake should be limited to 45% of total calories
**ALLOWED WEIGHT GAIN**

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

**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.
- Multiple daily injections is preferred for better glycaemic control.
- Use of short acting and long acting analogues – reduces the risk of hypoglycaemia.
- Short acting analogue will be able to control the post prandial hyperglycaemia.

**INITIATING INSULIN**

<table>
<thead>
<tr>
<th>Glycaemic Abnormality</th>
<th>Suggested Insulin Type and Dose</th>
</tr>
</thead>
</table>
| FPG >5.1 mmol/L, 3-hour postprandial >7.8 mmol/L, 2-hour postprandial >6.7 mmol/L | • Start 0.2 units/kg of intermediate-acting insulin at bedtime, increase by 2 units every 3 days until targets are reached.  
• 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 TID, consider adding 6-10 units intermediate-acting insulin in the morning and titrate accordingly until targets are achieved. |
In 2 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.

Postpartum Care

- Insulin requirement drops immediately after delivery by 60-75%.
- In breast-feeding, if glycaemic control is inadequate with diet therapy alone, insulin therapy should be continued at a lower dose.
- In non-breast-feeding mothers, OAD agents can be continued.
Postpartum Care

- Low dose metformin can be safely used in nursing mothers.
- Patients should be counseled regarding appropriate contraception.
- Women with GDM should be informed of the risk of GDM in future pregnancies and advised to have a OGTT when planning future pregnancies.
- Women with a history of GDM should have annual screening for diabetes.

Summary

- Diabetes in pregnancy is associated with maternal and foetal outcomes.
- Important to screen at the right time.
- Pre-conception counselling is important in pre-existing diabetes.
- It is important to achieve the glucose targets without hypoglycaemia.
- Insulin therapy is still the mainstay of treatment.
- During post partum, adjustment of insulin and OHA should be done with a repeat OGTT in women with GDM.
Case Study

diabetes in special populations 1
Case 1

A 27-year-old Malay woman has T2DM and hypertension for 5 years.

Recently she got married and wishes to start a family immediately.

Her medications are:
- Diamicron MR 120 mg daily
- Metformin 1g bd
- Telmisartan 40 mg daily

Patient is obese with suboptimal diabetes control.

Is she allowed to conceive?

What general advice should she be given?

- The patient has well controlled hypertension but poor control of glucose.
- A preconception counselling should be performed.
- The target A1c should be less than 6.5%.
- The patient should also be informed of the issue with her weight and make an effort to reduce the it.
- The antihypertensive medications should be reviewed and change to other medications permitted in pregnancy (ARB can be changed to nifedipine, labetolol, methyldopa, clonidine or hydralazine)
Questions

- How would you manage her blood glucose?
  - Advise to exercise and also refer to the dietitian
  - Discuss with the patient the need to intensify her diabetes treatment
  - Either start patient on basal insulin
  - Switch to basal-bolus insulin regime and stop the OAD

Case 2

A 30-year-old Indian lady attended antenatal clinic at 14 weeks of gestation.

No prior medical illness.

Both parents have T2DM

Her pre-conception BMI was 28 kg/m².

At 14 weeks gestation, should you screen for GDM?

- She has risk factors for GDM (BMI, FH) so should be screened early for GDM

Results of OGTT:

- FBS – 5.0 mmol/L
- 2 hours post glucose challenge – 7.7 mmol/L
**SLIDE 7**

Does the patient have Gestational Diabetes Mellitus?

- No, OGTT showed normal result.

What is the further plan?

- As she has risk factors, a repeat OGTT should be performed at 4-6 weeks later, if normal to repeat at 24-28 weeks of gestation.

**SLIDE 8**

On Follow-up...

At 20 weeks of gestation, mOGTT was again normal.

At 28 weeks of gestation, repeat OGTT showed:

- FPG 5.1 mmol/L
- 2 hour post glucose challenge – 8 mmol/L

**SLIDE 9**

Is she diabetic now?

- Yes

What is the management?

- She has gestational diabetes.
- She should be given dietary advice to control the blood sugar.
- It is important for her to monitor the blood glucose and initiate insulin if the target blood glucose levels are not achieved within 1-2 weeks.
Case 3

A 35-year-old Chinese woman with T2DM.
No other medical illness.
On Metformin 1g bd.
Her latest A1c – 6.5%
Recently married and now pregnant at 6 weeks POA.

Patient expresses her wish to continue with metformin. What will be the next step?

- She has a good control of diabetes with metformin.
- Metformin has been shown to be safe during pregnancy. However the use of metformin in pregnancy is off labelled. The above should be conveyed to the patient before any decision is made to continue with the therapy.

On Follow-up...

A month later her blood sugar started to increase

- FBS – ranges from 4.8-5.2 mmol/L
- Pre-lunch – ranges from 5-5.8 mmol/L
- 2 hours post lunch – ranges from 6-7.2 mmol/L
- Pre-dinner – ranges 5-6.0 mmol/L
- 2 hours post dinner- ranges 6-6.9 mmol/L

She was initiated on insulinard 10 u in the morning.

How do you monitor this patient?

- The patient should monitor the blood glucose regularly.
- The fasting and pre-meals and postprandial blood glucose monitoring should be done.
At 16 weeks, the blood glucose monitoring revealed the following results:

- FBS – ranges from 4.8-5.2 mmol/L
- Pre-lunch – ranges from 5-5.3 mmol/L
- 2 hours post lunch – ranges from 6-8.7 mmol/L
- Pre-dinner – ranges 5-5.4 mmol/L
- 2 hours post dinner - ranges 6-6.7 mmol/L

The pregnancy is at 16 weeks. As the pregnancy progresses, there is possibility of increasing insulin need.
The 2 hours post lunch is not at target.

What should you do next?

- A bolus of short-acting insulin should be started at lunch with a dose of 6 u and titrate to target.
diabetes in special populations 2
During Ramadan, eating habits change in many ways, not only do mealtimes change, but patterns of meals. There is an increase in post prandial physical activity during the night times associated with observation of religious practices (Tarawih). Psychological changes due to the
general spiritual atmosphere during Ramadan, which create a feeling of inner well-being, are also important.

SLIDE 4

Things Happened During Ramadan

- This include meal timing, total calories, food type and consistency.
- Prior to the month of Ramadan, people usually take 3 major meals (breakfast, lunch, dinner/supper)
- *This will change to 1-6 two meals Regular iftar and suhur. Iftar will be around 6:00 pm and Suhur will be around 3:00 am.

SLIDE 5

Things Happened During Ramadan

- Increased in post prandial physical activity during the night times associated with Tarawih.
- Psychological changes due to the general spiritual atmosphere during Ramadan, which create a feeling of inner well-being

SLIDE 6

Surah Al-Baqarah: 183-184

- ......Observing As-Saum (the fasting) is prescribed for you as it was prescribed for those before you, ....
- ...... but if any of you is ill or on a journey, ...... And as for those who can fast with difficulty, (e.g. elderly, etc).......
- This exemption represent more than simple permission not to fast; the prophet Mohamad said "God like his permission to be fulfilled, as he likes his will to be executed"
**Major Risks associated with Fasting in Patients with Diabetes**

- Hypoglycemia
- Hyperglycemia
- DKA
- Dehydration and thrombosis

---

**Self-reported Hypoglycaemia Before and During Ramadan**

<table>
<thead>
<tr>
<th>Overall population</th>
<th>type 1 DM</th>
<th>type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Ramadan</td>
<td>During Ramadan</td>
</tr>
<tr>
<td><strong>Non-severe hypoglycaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (4.9)</td>
<td>1.7 (3.0)</td>
</tr>
<tr>
<td>p</td>
<td>SS (p &lt; 0.001)</td>
<td>NS (p = 0.29)</td>
</tr>
<tr>
<td><strong>Severe hypoglycaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.03 (0.1)</td>
<td>0.14 (0.6)</td>
</tr>
<tr>
<td>p</td>
<td>SS (p = 0.0174)</td>
<td>SS (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

*: requiring hospitalisation

---

**Severe hyperglycaemia before and during Ramadan**

<table>
<thead>
<tr>
<th>Frequency of episodes requiring hospitalisation per month</th>
<th>DM-type 1</th>
<th>DM-type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Ramadan</td>
<td>During Ramadan</td>
</tr>
<tr>
<td>Overall population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS (p = 0.16)</td>
<td>SS (p &lt; 0.001)</td>
</tr>
<tr>
<td><strong>Population who fasts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>p</td>
<td>SS (p &lt; 0.001)</td>
<td>SS (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>
EPIDIAR study in 2001 revealed that 43% and 76% patients with T1DM and T2DM fast at least 15 days during Ramadan, leading to 40-50 million people with diabetes fast in Ramadan. Marked differences are observed between countries particularly in those with T1DM which varied from 9.4% in Morocco and 77% in Saudi Arabia. For T2DM subjects who fasted at least 15 day varied between 57.6% in Turkey and 89.8% in Malaysia and Bangladesh.
**Categories of risks in patients with type 2 diabetes who fast during Ramadan**

**Very high risk**
- Severe hypoglycemia in last 3/12
- History recurrent hypoglycemia
- Hypoglycemia unawareness
- Poor glycemic control
- Acute illness
- Hyperosmolar in last 3/12
- Intense physical labor
- Pregnancy
- Chronic dialysis

**High risk**
- Moderate hyperglycemia
- Renal insufficiency
- Advanced macrovascular complication
- Living alone treated with SU/insulin
- Comorbid condition
- Old age with ill health
- Drug that may effect mentation

**Moderate risk**
- Well control patient treated with meglitinide

**Low risk**
- Diet alone, metformin/ TZD/DPP4-ii/AGI
SLIDE 15

RAMADAN GUIDELINES FOR PATIENTS WITH DIABETES MELLITUS Type 2

Patients with one or more of the following are advised not to fast:

- Conditions related to diabetes:
  - Nephropathy with serum creatinine more than 1.5 mg/dL
  - Severe retinopathy
  - Autonomic neuropathy: gastroparesis, postural hypotension
  - Hypoglycemia unawareness
  - Major macrovascular complications: coronary and cerebrovascular
  - Recent hyperosmolar state or DKA
  - Poorly controlled diabetes (Mean Random BG > 300)
  - Multiple insulin injections per day

- Physiological conditions:
  - Pregnancy
  - Lactation

SLIDE 16

RAMADAN GUIDELINES FOR PATIENTS WITH DIABETES MELLITUS Type 2

Patients with one or more of the following are advised not to fast:

- Co-existing major medical conditions such as:
  - Acute peptic ulcer
  - Pulmonary Tuberculosis and uncontrolled infections
  - Severe bronchial asthma
  - People prone to urinary stones formation with frequent Urinary Tract Infections
  - Cancer
  - Overt cardiovascular diseases (recent MI, unstable angina)
  - Severe psychiatric conditions
  - Hepatic dysfunction (liver enzymes > 2 x ULN)

SLIDE 17

Management

General consideration

- Individualisation
- Frequent monitoring
- Nutrition
- Breaking the fast
Management
General Consideration

Nutrition
- Should not differ significantly from healthy balance diet
- Maintain constant body mass
- More complex CHO at predawn meal
- Increased fluid during non fasting period
- Predawn meal taken as late as possible before the start of daily fasting

Management
General Consideration

Exercise
- May maintain normal physical activity
- Avoid excessive physical activity in particular few hour before sunset meal
- Terawih prayer as part of daily exercise

Management
Pre-Ramadan Assessment and Education

- Status of glycaemia, BP and lipid
- Specific advice (patient and family)
  - Diet
  - Medication
  - Self care (SMBG, hypoglycaemia kit, exercise)
**Management**
**General Consideration**

**Breaking Fast**
- Should always and immediately broken;
  - Symptomatic
  - Asymptomatic
    - BS < 3.3 mmol/l
    - BS < 3.9 mmol/l in first few hours of starting fasting
    - BS > 16.7 mmol/l

---

**Slide 22**

**Patients agree with breaking fast during Ramadan**

<table>
<thead>
<tr>
<th>Country</th>
<th>Type 1 DM (%)</th>
<th>Type 2 DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>69</td>
<td>49</td>
</tr>
<tr>
<td>Egypt</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>India</td>
<td>62</td>
<td>47</td>
</tr>
<tr>
<td>Indonesia</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Jordan</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>Lebanon</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Malaysia</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Morocco</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Pakistan</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Turkey</td>
<td>49</td>
<td>49</td>
</tr>
</tbody>
</table>

Same trend in most countries

- 73%
- 55%

---

**Slide 23**

**Management of T2DM**

**Diet controlled patients**
- Risk of fasting is quite low
- Risk for occurrence of post prandial hyperglycemia
- Distribute the calorie to >2 smaller meal during non-fasting hours
Management of T2DM

T2DM with Metformin
- May safely fast
- 2/3 total daily dose immediately before sunset meal
- 1/3 before pre-dawn meal

Management of T2DM

T2DM with TZD/DPP-4i/GLP-1 RA/SGLT2i/AGI
- No dose change required
- Low risk of hypoglycemia

Management of T2DM

T2DM with SU
- Newer SU is effective with less hypoglycaemia
- Avoid glipclamide
- Chlorpropamide is absolutely contraindicated
**Insulin Adjustments During Ramadan**

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

**Recommendations**

**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)
Case Study

diabetes in special populations 2
Case 1

A 68-year-old man with underlying:
- Type 2 Diabetes mellitus for 20 years
- Hypertension
- Dyslipidemia

His current medications are:
- Metformin 1 g BD
- Diamicon MR 90 mg daily
- Amlodipine 10 mg daily
- Lovastatin 40 mg daily

During follow-up, he claimed had multiple episodes of low blood sugar ~ 2-3x per week.

He is compliant to his medications & diet.

Investigations:
- A1c : 8.1%
- FBS : 5.9 mmol/L
- Renal profile: 135/4.1/5/80
- FSL : TG 2.5 mmol/L, TC 5.9 mmol/L, HDL-C 0.8 mmol/L, LDL-C 3.2 mmol/L
- UFE/EME : protein ++
- SMBG:
  - FBS : 4-6.2mmol/L
  - Post-meal: >10 mmol/L

He expresses his desire to fast in Ramadan.

How you categorise him in term of his risk of fasting during Ramadan?
- High risk

Despite your recommendation, he insist on fasting. What is your advice?
SLIDE 4

Advice
- Must ensure that he has adequate intake during sahur
- Reduce the dose of diamicron to 60 mg, to be taken at breaking of fast (iftar)
- Continue metformin 1 gm at sahur and iftar
- Adequate fluid intake at sahur
- Monitor for daytime hypoglycaemia and hyperglycaemia with SBGM at
  - Pre sahur
  - Post sahur
  - Pre iftar
  - Post iftar or bedtime
- Break the fast promptly with any signs of hypoglycaemia

SLIDE 5

Case 2

A 50-year-old man with underlying T2DM / HPT. No complications.

Medications:
- Mixtard 30/20 unit bd
- Metformin 1 g bd
- Perindopril 8 mg od
- Simvastatin 20 mg on

BP : 130/80 mmHg
A1c : 7.2%

SLIDE 6

Identify patient risk category of fasting.
- High risk

Patient intends to fast despite your advice.

How do you manage this patient?
- Educate on risks:
  - hypoglycaemia, hyperglycaemia and dehydration
- SMBG
- When to end fast
- Medication
**Slide 7**

How to take his medications?

<table>
<thead>
<tr>
<th>CURRENT TREATMENT</th>
<th>FASTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIXTARD 30/20 UNIT BD</td>
<td>1. Reverse doses: morning dose at iftar &amp; evening dose at sahur</td>
</tr>
<tr>
<td></td>
<td>2. Reduce dose at sahur by 20-50% to prevent daytime hypoglycaemia</td>
</tr>
<tr>
<td>METFORMIN 1 g BD</td>
<td>Take 1 g at iftar and sahur</td>
</tr>
</tbody>
</table>

**Slide 8**

When to do SMBG?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Timing and frequency SMBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anti-diabetic (OAD)</td>
<td>Monitor when symptomatic¹</td>
</tr>
<tr>
<td>Insulin</td>
<td>Diabetic patients who are in the moderate to high risk categories are advised to monitor their blood glucose 5 times per day²:&lt;br&gt; - Pre-meal and 2-hour post pre-dawn meal (sahur)&lt;br&gt; - Mid-day&lt;br&gt; - Pre-meal and 2-hour post sunset meal (iftar)&lt;br&gt; - Bedtime</td>
</tr>
</tbody>
</table>

**Slide 9**

When to end fast?

Conditions to stop fasting:

- Blood glucose <3.3 mmol/l at anytime during the fast¹
- Blood glucose <3.9 mmol/l in the first few hours of fasting (especially if the patient is taking sulfonylureas, meglintindes, or insulin)²,³
- Blood glucose >16.7 mmol/l⁴
- Experience symptoms of hypoglycaemia (patients without SMBG)⁴
- Symptoms suggestive of severe dehydration such as syncope and confusion⁴
SLIDE 10

What is your advice regarding his diet?

- Never skip sahur (dawn meal)
- Do not delay “berbuka”
- Supper after Tarawih can be taken as replacement of pre-bed snack
- Include fruits and vegetables at both sahur and iftar
- Limit fried and fatty foods
- Limit intake of highly salted foods to reduce risk of dehydration
- Drink adequately at sahur, choose sugar-free drinks, aim for 8 glasses per day
- Avoid excessive binging of carbohydrates during non-fasting period

SLIDE 11

What is advice regarding his physical activity?

- Light and moderate intensity exercise on a regular basis\(^1\)\(^2\)
- Avoid rigorous exercise during fasting time\(^1\)\(^2\)
- The timing of exercise is preferably 1-2 hours after the break of fast\(^1\)\(^2\)
- Performance of Tarawih night prayers\(^3\)
diabetes in special populations 3
**Introduction**

- T2DM is rapidly increasing among the adolescents (ages 12-18 years): rising sedentary lifestyles and prevalence of obesity.

- Commonest form of diabetes in this age group in many countries
  - Japan, the incidence rate of T2DM in children <18 years from 1981 to 1990 - 4.1/100,000 person-years versus 1.5 to 2.0/100,000 person-years for T1DM.
  - Common in adolescents coinciding with physiologic pubertal insulin resistance.

---

**Lifestyle Practices and Obesity in Malaysian Adolescents**

Pey Soo Tee 1,2, Abdulkarim Marhat-Ahmed 1, Mohamed Essam Ali 1, Andrew P. Hiles 3 and Low Huan Fei 4

Table 1. General characteristics and body composition profiles (mean ± SD) of adolescent boys and girls by ethnicity, n = 454.

<table>
<thead>
<tr>
<th></th>
<th>Malay (n = 286)</th>
<th>Chinese (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>13.6 ± 1.9</td>
<td>13.2 ± 1.9</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>52.5 ± 16.3</td>
<td>52.9 ± 11.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159.8 ± 5.9</td>
<td>160.5 ± 5.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.7 ± 4.2</td>
<td>20.7 ± 4.2</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>65.1 (10)</td>
<td>65.6 (10)</td>
</tr>
<tr>
<td>Normal</td>
<td>78.3 (71)</td>
<td>78.6 (70)</td>
</tr>
<tr>
<td>Overweight</td>
<td>21.1 (21)</td>
<td>21.3 (21)</td>
</tr>
<tr>
<td>Pre-pubertal</td>
<td>0.03 ± 0.36</td>
<td>0.03 ± 0.36</td>
</tr>
<tr>
<td>Pubertal</td>
<td>7.8 (13)</td>
<td>7.6 (12)</td>
</tr>
<tr>
<td>Pre-pubertal</td>
<td>15.6 (18)</td>
<td>15.8 (20)</td>
</tr>
<tr>
<td>Dietary energy intake (kcal/m²-day)</td>
<td>2,440 ± 2,170</td>
<td>2,150 ± 1,840</td>
</tr>
</tbody>
</table>

---

**Primary Factors Contributing to Development of T2DM in Children**

- Familial history
- Other genetic factors
- Ethnic background
- Female gender
- Accelerated beta cell failure
- Insulin resistance
- Obesity (visceral)
- Prenatal environmental factors
- Sedentary lifestyle
- Puberty
Atherosclerosis begins in Childhood


T2DM in childhood predisposes for earlier onset of nephropathic disease

Pavkovic ME, et al. JAMA, 2006

A National Database on Children and Adolescent with Diabetes (e-DICARE): Results from April 2006 to June 2007

Table 1: Number and Proportion of Cases of Diabetes Mellitus amongst those with known Basal Diagnosis, e-DICARE: April 2006-June 2007

<table>
<thead>
<tr>
<th>Basal Diagnosis</th>
<th>Type 1DM</th>
<th>Type 2DM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>100</td>
<td>90</td>
<td>190</td>
</tr>
<tr>
<td>Clinical</td>
<td>50</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>30</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2: Median and Mean of HbA1c by Type of Diabetes Mellitus amongst those with known HbA1c study, e-DICARE: April 2006-June 2007

<table>
<thead>
<tr>
<th>Type 1DM</th>
<th>Type 2DM</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>5.9 (1.9)</td>
<td>5.9 (1.9)</td>
<td>5.5 (1.6)</td>
</tr>
</tbody>
</table>
Table 2.4.4.2 Glycaemic control of T1DM patients in the past 12 months, Diccare 2006-2008 (N=48)

<table>
<thead>
<tr>
<th>Profiles</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>47.5</td>
<td>12 (25.0)</td>
</tr>
<tr>
<td>7.0 - &lt; 8.0</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>9.0 - &lt; 10.0</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>28 (54.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 2.4.4.1 Glycaemic control by age group of T1DM patients in the past 12 months, Diccare 2006-2008 (N=48)

<table>
<thead>
<tr>
<th>Profiles</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median (IQR 1st - 3rd)</th>
<th>Min, max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48</td>
<td>10.8 (3.5)</td>
<td>11.4 (IQR 7.5 - 13.5)</td>
<td>5.4, 19.7</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>3</td>
<td>7.2 (1.5)</td>
<td>6.6 (IQR 6.6 - 7.5)</td>
<td>6.6, 8.4</td>
</tr>
<tr>
<td>5-&lt;10 years</td>
<td>10</td>
<td>10.7 (3.3)</td>
<td>11.9 (IQR 7.2 - 13.3)</td>
<td>5.4, 15.1</td>
</tr>
<tr>
<td>10-&lt;15 years</td>
<td>22</td>
<td>11.1 (3.6)</td>
<td>10.9 (IQR 8.2 - 13.9)</td>
<td>6.3, 19.7</td>
</tr>
<tr>
<td>15-&lt;20 years</td>
<td>13</td>
<td>11.3 (3.5)</td>
<td>12.1 (IQR 7.8 - 14.3)</td>
<td>9.0, 17.1</td>
</tr>
</tbody>
</table>

Introduction

- 15-40% of T2DM patients have T1DM-associated pancreatic autoantibodies - less overweight, younger, have higher A1c and more rapid development of insulin dependence (usually by 3 years duration).

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

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

Screening and Diagnosis

- Symptomatic or
- If they are overweight (BMI >85th percentile for age and sex, or weight >120% of ideal)
- Have two or more of the following risk factors:
  - Family history of T2DM in first- or second-degree relative.
  - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, PCOS).
  - 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. A glucose load of 1.75 g/kg body weight (maximum of 75 g) for OGTT is used.
**SLIDE 10**

**Diagnosis**

- Fasting insulin and C-peptide - aid diagnosis.
- Measurement 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.

---

**SLIDE 11**

**Diagnosis**

- 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.

---

**SLIDE 12**

**Management**

- Management of T2DM in the adolescents - involve the patient and his/her family, emphasising healthy rearing patterns and parental modelling 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.
**SLIDE 13**

**Preventive Measures**
1. All foods and beverages served in schools meet Dietary Guidelines.
2. Increasing access to high-quality, affordable foods through new or improved grocery stores and healthier corner stores and bodegas.
3. Increasing the time, intensity, and duration of physical activity during the school day.
4. Increasing physical activity by improving the built environment in communities.
5. Using pricing strategies—both incentives and disincentives—to promote the purchase of healthier foods.
6. Reducing youths’ exposure to the marketing of unhealthy foods through regulation, policy, and effective industry self-regulation.

**SLIDE 14**

**TODAY Study**

**Treatment T2**
- Randomized clinical trial with a pre-randomization run-in period
  - 704 patients at 15 clinical centers
  - 3 treatment regimens
    - Metformin + Placebo
    - Metformin + Rosiglitazone
    - Metformin + Intensive Lifestyle Program
  - At treatment failure: Standardized approach to insulin initiation
- Primary outcome: Time to failed glycemic control
- Inclusion criteria
  - Age 10–17 years
  - Duration of diabetes <2 years
  - BMI ≥ 85th percentile

**SLIDE 15**

**Treatment T2: The TODAY Trial**

<table>
<thead>
<tr>
<th>Mean ± SD or %</th>
<th>Medications at Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>14.3 ± 2.0</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19.6%</td>
</tr>
<tr>
<td>African American</td>
<td>37.4%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>32.2%</td>
</tr>
<tr>
<td>Native American</td>
<td>5.5%</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>5.3%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>36.2 ± 7.9</td>
</tr>
<tr>
<td>25 - 71</td>
<td></td>
</tr>
<tr>
<td><strong>BMI Z-score</strong></td>
<td>+2.3 ± 0.5</td>
</tr>
</tbody>
</table>

**Characteristics of adolescents and youth with recent-onset type 2 diabetes in the TODAY cohort at baseline.**

**Slide 16**

A Clinical Trial to Maintain Glycemic Control in Youth with Type 2 Diabetes

**Slide 17**

Treatment T2: The TODAY Trial Study Results

**Slide 18**

Pharmacotherapy

- Treatment of T2DM in adolescents follow the same rationale as does treatment in adults.

- The safety and efficacy of OADs in adolescents have not been established.

- 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.

- 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.
Pharmacotherapy

- 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.
- In adolescents, long-acting or intermediate acting insulin may be added at a dose of 0.5 u/kg at bed-time.

Conclusion

- 1. Obesity is on the rise among our children
- 2. As a result type 2 DM is increasing
- 3. Treatment is difficult
  - Compliance is poor
  - Numerous psychological issues
  - Limited studies on existing and new anti-diabetic agents
  - Most end up on insulin with all it’s inherent issue
  - Increase rate of complications
Case Study

17

diabetes in special populations 3
Miss SM, a 15-year-old school girl.

Previously, she expressed her frustration with her increased body weight. However, for the last 3 months she noticed a marked weight loss, associated with feeling tired, increase thirst, urinary frequency and feeling hungry throughout the day.

Mother had GDM when she was pregnant with SM and 5 years later developed full blown T2DM (30 years old).

Mother is worried and brought her to the nearest Klinik Kesihatan.

**Examination/Investigations**

- Lethargic looking
- Fungal infection over both groins
- BP 108/80 mmHg
- Weight: 86 kg; Height: 165 cm, BMI = 31.6 kg/m²
- FBG = 16.1 mmol/L; A1c = 15.8%
- Urine ketone trace; urine protein negative
- Serum creatinine = 60 µmol/L

**Would you consider any further assessment and investigations?**

- Fundoscopy
  - No diabetic retinopathy
- Fasting lipid profile
  - TG = 1.8 mmol/L
  - HDL-chol = 0.9 mmol/L
  - LDL-chol = 4.5 mmol/L
- Anti-GAD antibody
  - To rule out type 1 diabetes
What is the diagnosis?
Type 2 diabetes mellitus
Reasons:
- No ketone
- Strong family history
- Obese
- Dyslipidaemia
- Chronicity / long-standing symptoms

How would you manage her?
Her treatment priority is controlling her blood glucose
- Initiate insulin therapy (basal-bolus or bd premixed regimens) 0.5 u/kg/day
  - Plus
  - Metformin 500 mg OD, titrate up to 1 g BD
  - Monitor SMBG
  - Refer dietitian and diabetic educator for lifestyle modifications
Onset of T2DM at early age – glycaemic legacy if BG not controlled for long periods

Estimated glycaemic legacy of patients recruited in VADT

---

Treatment of other co-morbidities

- Dyslipidaemia
  - Start on statin
- Treat fungal infections in groins
  - Anti-fungal agent – miconazole cream

What is her glycaemic target?

A. < 6.0%
B. 6.0% - 6.5%
C. 6.5% - 7.0%
D. 7.0% - 7.5%
E. 7.5% - 8.0%
Why?

- Individualised glycaemic targets\(^1\)
- Long life expectancy
- Long term safety of treatment
- A1c on target without or minimal hypoglycaemia
- Other factors favouring stringent control:
  - Strong support system
  - Lack of co-morbidities/complications
  - Recent diagnosis


How do you help her to achieve her glycaemic control target?

- Aim: preserve beta-cell functions and improve insulin sensitivity
- Diabetes care education
- Dietary and lifestyle modification advice
- Self-monitoring blood glucose
- Weight loss – target weight loss of 4-8 kg (5-10%) in 6 months
- Pharmacotherapy

What is the appropriate choice of therapy for her?

A. Lifestyle alone
B. Lifestyle and insulin
C. Lifestyle and metformin
D. Lifestyle, metformin and insulin
E. Lifestyle, metformin and sulphonylureas
A. Lifestyle alone: FBG 16.1 mmol/l; A1c 15.8%; LDL 4.5 mmol/l - glucolipotoxicity
B. Lifestyle and insulin: highest A1c efficacy; high hypoglycaemic risk; weight gain
C. Lifestyle and metformin: high A1c efficacy; low hypoglycaemic risk; weight neutral/loss; Side-effects – GI symptoms; low cost
D. Lifestyle, metformin and insulin: metformin and lifestyle may offset weight gain of insulin
E. Lifestyle, metformin and sulphonylureas: not approved or recommended for use in this age population

SM was put on mixtard 20 units bd + metformin 1 g bd in addition to lifestyle modification.

2 months later...

SM became withdrawn, irritable, rebellious.
Hypoglycaemia 3-4 times a week.
Frequently unable to finish her homework from school.
Frequently missed mixtard injections.
SMBG monitoring sparingly (when forced by mum):
  • Prebreakfast 11.0 mmol/L; post-lunch 12.8 mmol/L

Mum was worried.

What is the best options for her?

A. Lifestyle + metformin
B. Lifestyle + metformin + rosiglitazone
C. Lifestyle + metformin + rosiglitazone + basal insulin
D. Lifestyle + metformin + GLP-1
E. Lifestyle + metformin + Insulin pump
A. Lifestyle + metformin: FBG > 11.0 mmol, post-lunch > 11.0 mmol/l; residual glucolipotoxicity
B. Lifestyle + metformin + rosiglitazone: poor response in presence of glucolipotoxicity
C. Lifestyle + metformin + rosiglitazone + basal insulin: possible best option
D. Lifestyle + metformin + GLP-1: not approved for use in this age group
E. Lifestyle + metformin + insulin pump

prevention of type 2 diabetes mellitus
SLIDE 1

Individuals at risk

Those at risk include those with IGT or IFG, but also those with:

- Family history of diabetes (1st degree relatives)
- GDM
- Hypertension
- Vascular disease
- Dyslipidaemia
- Obesity/overweight with central obesity
- PCOS

SLIDE 2

Diagnostic values for Pre-Diabetes

1) Based on OGT

<table>
<thead>
<tr>
<th>Based on OGT</th>
<th>Fasting (0 hr)</th>
<th>2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG</td>
<td>6.1 – 6.9 mmol/L</td>
<td>-</td>
</tr>
<tr>
<td>IGT</td>
<td>-</td>
<td>7.8 – 11.0 mmol/L</td>
</tr>
</tbody>
</table>

2) Based on HbA1c

- Pre-diabetes 5.6 – 6.2 %

Adapted from Table 3 & 4 (page 7)

SLIDE 3

Scientific Evidence

- There is well documented evidence → interventions significantly REDUCE the conversion of abnormal glucose tolerance (IFG + IGT) to overt T2DM
  - Da Qing IGT & Diabetes Study (China)
  - Diabetes Prevention Study (Finland)
  - Diabetes Prevention Program (USA)
  - Indian DPP (India)
  - STOP NiIDDM (Europe, Canada)
**Slide 4**

**Scientific Evidence (cont.)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifestyle</td>
</tr>
<tr>
<td>Da Qing665</td>
<td>31-46</td>
</tr>
<tr>
<td>DPS67</td>
<td>58</td>
</tr>
<tr>
<td>DPP45</td>
<td>58</td>
</tr>
<tr>
<td>Indian DPP471</td>
<td>26.5</td>
</tr>
<tr>
<td>Stop NIDDM472</td>
<td>-</td>
</tr>
</tbody>
</table>


**Slide 5**

**Intervention**

- Diet and moderate intensity physical activity (that result in a modest weight loss of 5-7% of body weight) are the mainstay of therapy.
- Weight loss remains a priority in prevention of T2DM.
- In addition, Metformin should be considered:
  - Those at very high risk (IFG + IGT, plus other risk factors)
  - Fail lifestyle therapy after 6 months.
- Behavioural and lifestyle modification have shown long-term effects on prevention of diabetes beyond the period of active intervention475, 476, 477.


**Slide 6**

**Intervention (cont.)**

- Other pharmacological agents than can be used:
  - Acarbose
  - Orlistat
  - Rosiglitazone
    → All the above drugs – off label use
- Use of other agents (ACE-Is, ARBs and statins are not recommended solely for the purpose of primary prevention).
Monitoring

- Annual assessment / monitoring for glucose tolerance status is recommended
- Screening and appropriate management of other modifiable cardiovascular risk factors is suggested

Summary

- In individuals with IGT, a structured program of lifestyle modification that includes moderate weight loss and regular physical activity has been shown to reduce the risk of T2DM
- Lifestyle intervention programmes have greater efficacy than pharmacological intervention, and are more practical and cost effective, making its implementation possible in any Primary healthcare setting

Recommendations:
Prevention of Type 2 diabetes mellitus

1. In patients with IFG / 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 progression to T2DM
   [Grade A]

2. Use of pharmacological intervention such as metformin can be considered in those who fail lifestyle intervention (after 6 months)
   [Grade C]
Case Study

prevention of type 2 diabetes mellitus
A 46-year-old woman comes for routine medical check-up. She has hypertension for the past 2 years, on atenolol 50 mg daily. Otherwise, no complaints.

She has GDM in her last pregnancy 15 years ago, managed with diet. Postpartum, did not do OGTT.

FH – both parents have T2DM.

Physical examination:
- Weight 72 kg, height 160 cm, BMI 28.1 kg/m²
- Waist circumference 88 cm, BP 140/95 mmHg.
- CVS – no cardiomegaly. No other abnormality.

**Q1: What is her risk of developing T2DM?**
- This patient has very high risk for developing T2DM
  - History of GDM
  - Strong FH of T2DM
  - Metabolic syndrome phenotype
  - Increased waist > 80 cm
  - Hypertension

**Q2: What investigations will you order?**
- FBS
- OGTT
- A1c

**Investigations:**
- Fasting glucose 6.5 mmol/L
- Renal function Normal
- Total cholesterol 5.6 mmol/L
- HDL-C 1.0 mmol/L
- LDL-C 3.3 mmol/L
- TG 2.9 mmol/L

**Q3: Comment on the results**
- IFG
- Metabolic dyslipidaemia – low HDL, high TG
- Recommend OGTT in view of IFG
Q4: What will you do next?
A. OGTT
B. A1c
C. No need anything else, treat with lifestyle modifications

If you did
1. OGTT
   • 6.5 / 9.1 mmol/L
2. A1c
   • 5.9%

Q5: Comment on the results
• Pre-diabetes
• Combined IFG + IGT

My preference would have been OGTT – understanding the problems with doing the 2-hr OGTT, but we get a clearer idea of the severity of the glucose intolerance. Also important to do either OGTT / A1c to ensure she has not become overtly diabetic.
Q6: How will you manage her?
1. Start her on lifestyle intervention alone
2. Start her on metformin + lifestyle intervention
3. Start her on acarbose + lifestyle intervention
4. Send her to bariatric surgeon

Take history of what she has been trying to do. Has she been trying to lose weight already, but has been unsuccessful.

If she has been trying lifestyle already of at least 6 months duration or more, then answer # 2 is more appropriate; # 3 – acarbose has not been given an indication for use for prevention of DM; # 4 – no data to recommend this course of action.

Q7: Is she has not started any lifestyle intervention in the past, what specific lifestyle goals will you advise?
1. Refer Dietitian
   • Aim for weight loss 4.0 – 5.0 kg (5-7% body wt)
2. Physical activity
   • 30 mins moderate intensity x 5/week

Q8: Is she has already tried lifestyle intervention for >1 year in the past, what will you advise?
1. Initiate pharmacological intervention, in addition to reinforcing lifestyle modification
   • Start metformin 500 mg BD → titrate as tolerated to metformin 850 mg BD

Metformin dose used for DPP was metformin 850 mg BD. But for Indian DPP, metformin dose was lower.
She was started on Metformin 850 mg BD.

2 years later, her weight was 68 kg.
Repeat FPG 6.0, A1c 5.7 %

Q9: What will you do?
1. Continue metformin
2. Stop metformin

Metformin should be continued.
- She is still overweight – BMI 26.6 kg/m²
- Her A1c is still in pre-diabetic range
APPENDIX 1

template for training program
### Template for Training Programme

**Clinical Practice Guidelines on the Management of Type 2 Diabetes Mellitus 2015**

**Day 1**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00-8.30</td>
<td>Registration of Participants</td>
<td></td>
</tr>
<tr>
<td>8.30-8.45</td>
<td>Welcoming Address, Introduction of the Workshop &amp; Pre-Test Questions</td>
<td>Chairperson:</td>
</tr>
<tr>
<td>8.45-9.00</td>
<td>Overview of Type 2 Diabetes Mellitus (T2DM) &amp; Revised CPG for the Management of T2DM 2015</td>
<td></td>
</tr>
<tr>
<td>9.00-9.30</td>
<td>Screening &amp; Diagnosis</td>
<td></td>
</tr>
<tr>
<td>9.30-9.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>9.45-10.00</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>10.00-10.15</td>
<td>Morning Tea Break</td>
<td></td>
</tr>
<tr>
<td>10.15-10.30</td>
<td>Targets for Control</td>
<td>Chairperson:</td>
</tr>
<tr>
<td>10.30-10.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>10.45-11.30</td>
<td>Medical Nutrition Therapy &amp; Low Glycaemic Index Diet</td>
<td></td>
</tr>
<tr>
<td>11.30-11.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>11.45-12.00</td>
<td>Physical Activity</td>
<td></td>
</tr>
<tr>
<td>12.00-12.15</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>12.15-12.30</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>12.30-14.30</td>
<td>Lunch &amp; Friday Prayer</td>
<td></td>
</tr>
<tr>
<td>14.30-15.15</td>
<td>Oral Anti-Diabetic Medications (Treatment Algorithms, Patient Specific Algorithms etc)</td>
<td>Chairperson:</td>
</tr>
<tr>
<td>15.15-15.30</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>15.30-16.15</td>
<td>Insulin Therapy &amp; Non-Insulin Injectables (GLP-1 RA)</td>
<td></td>
</tr>
<tr>
<td>16.15-16.30</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>16.30-16.45</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>16.45-17.00</td>
<td>Afternoon Tea Break</td>
<td></td>
</tr>
<tr>
<td>17.00-17.15</td>
<td>Diabetes with Hypertension</td>
<td>Chairperson:</td>
</tr>
<tr>
<td>17.15-17.30</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>17.30-17.45</td>
<td>Diabetes with Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>17.45-18.00</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>18.00-18.15</td>
<td>Diabetes with Obesity</td>
<td></td>
</tr>
<tr>
<td>18.15-18.30</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>18.30-18.45</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>18.45</td>
<td>End of First Day Session</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Topic</td>
<td>Speaker</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>8.30-9.00</td>
<td>Management Of Diabetic Emergencies 1: Hypoglycaemia</td>
<td></td>
</tr>
<tr>
<td>9.00-9.15</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>9.15-9.45</td>
<td>Management Of Diabetic Emergencies 2: DKA &amp; HHS</td>
<td></td>
</tr>
<tr>
<td>9.45-10.00</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>10.00-10.30</td>
<td>Management of Chronic Complications 1: Nephropathy, Retinopathy &amp; Neuropathy</td>
<td></td>
</tr>
<tr>
<td>10.30-10.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>10.45-11.00</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>11.00-11.15</td>
<td>Tea break</td>
<td></td>
</tr>
<tr>
<td>11.15-11.45</td>
<td>Management of Chronic Complications 2: IHD, CVA, Diabetic Foot &amp; ED</td>
<td></td>
</tr>
<tr>
<td>11.45-12.00</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>12.00-12.30</td>
<td>Diabetes in Special Populations 1: Hyperglycaemia in Pregnancy</td>
<td></td>
</tr>
<tr>
<td>12.30-12.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>12.45-13.00</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>13.00-14.00</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>14.00-14.30</td>
<td>Diabetes in Special Populations 2: Ramadan &amp; Elderly</td>
<td></td>
</tr>
<tr>
<td>14.30-14.45</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>14.45-15.00</td>
<td>Diabetes in Special Populations 3: Adolescents &amp; Children</td>
<td></td>
</tr>
<tr>
<td>15.00-15.15</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>15.15-15.45</td>
<td>Prevention of Type 2 Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td>15.45-16.00</td>
<td>Case Presentation</td>
<td></td>
</tr>
<tr>
<td>16.00-16.15</td>
<td>Q &amp; A</td>
<td></td>
</tr>
<tr>
<td>16.15-16.30</td>
<td>Closing Remarks &amp; Post-Test Questions</td>
<td></td>
</tr>
<tr>
<td>16.30-16.45</td>
<td>Afternoon Tea</td>
<td></td>
</tr>
<tr>
<td>16.45</td>
<td>End of Final Day Session</td>
<td></td>
</tr>
</tbody>
</table>
pre-test & post-test questionnaire
1. Which of the following is NOT a contributing factor in the pathogenesis of diabetes mellitus?
   A. Increased glucagon response to meals
   B. Increased renal reabsorption of glucose
   C. Increased hepatic production of glucose in the fasting state
   D. Reduced satiety hormones with meals
   E. Slow gastric emptying with meals

2. The following are true of the diabetes scenario in Malaysia except:
   A. More than half of adults are unaware they have the disease
   B. Up to 90% of those between 18 to 30 years are unaware they have diabetes
   C. The percentage of undiagnosed diabetes is highest among the Indians compared to the Malays and Chinese.
   D. Only a quarter of patients in government clinics have their diabetes under controlled
   E. A quarter of patients with diabetes in this country are on insulin.

3. In which of the following situations is the use of A1c (certified by the NGSP* and standardized to the Diabetes Control and Complications Trial) as a blood test to diagnose diabetes mellitus accurate:
   A. Children with suspected Type 1 Diabetes Mellitus
   B. Chronic Kidney Disease (GFR < 60 ml/min/1.73 m²)
   C. Hb E Beta (ß) Thalassemia
   D. Iron deficiency anaemia
   E. Pregnancy
   *National Glycohemoglobin Standardization Program

4. An A1c test result of 6.3% was reported in an asymptomatic patient who wanted to be screened for diabetes mellitus. What is your next course of action?
   A. Inform patient that he has diabetes mellitus
   B. Inform patient that he has prediabetes
   C. Request patient to come back another day for a repeat A1c test
   D. Request patient to come back in 3 months time for a repeat A1c test
   E. Request patient to come back another day for either a Fasting Blood Glucose test or Oral-Glucose Tolerance Test

5. The following are benefits of losing 5-10% of body weight within a 6-month period result in the reduction of the following except:
   A. 0.5% drop in A1c
   B. 3 mmol/l drop in FBG
   C. 5 mmHg drop in systolic and diastolic BP
   D. 1.0 mmol/l drop in in LDL-cholesterol
   E. 1.0 mmol/l drop in TG & 0.13 mmol/l increase in HDL-cholesterol

6. In the monitoring of patients with diabetes the following are true except:
   A. A1c should not be repeated more frequently than 3 months.
   B. Urinary albumin creatinine ratio (ACR) should be used to monitor those with overt proteinuria
C. A1c loses its reliability in those with CKD stages 4 and 5
D. Presence of proteinuria doubles the rate of progression to end-stage renal failure in patients with CKD stages 3 & 4.
E. In preventing cardiovascular diseases equal emphasis should be given to bring A1c, BP and Cholesterol to targets

7. **Which of the following contains the most amount of carbohydrate?**
   A. 1 bowl chicken and vegetable soup with 3 pieces of crackers
   B. 2 tablespoons scoops of rice and ½ bowl of fried long beans
   C. 1 piece roti canai and 1 small bowl of dhal curry
   D. 1 whole grilled fish and 3 slices of tomatoes
   E. 5 pieces of Yong Tau Fu

8. **Which of the following contains 15 grams of carbohydrate?**
   A. 300 ml fruit juice
   B. 1 scoop of rice
   C. 1 teaspoon of sugar
   D. 2 slices of white bread
   E. 2 packets of wholemeal crackers

9. **Which of the following significantly increases blood cholesterol level?**
   A. Beef steak
   B. Egg yolk
   C. Fried fish
   D. Fried king prawns
   E. Palm oil

10. **Which of the following results in a lower post-prandial blood glucose level (low glycaemic index)?**
    A. Spaghetti bolognaise
    B. Kuay teow soup
    C. Oats porridge
    D. Rice porridge
    E. Roti canai

11. **The following are signs of background retinopathy of diabetes mellitus except:**
    A. hard exudates
    B. hemorrhages
    C. macular oedema
    D. microaneurysms
    E. venous beading

12. A 55-year-old woman with diabetes presents with numbness in her hands and feet. She finds it difficult to turn pages of the newspapers and discriminating between different medication tablets. When walking she cannot feel her feet touching the floor.
    **What is the most likely diagnosis is:**
    A. Autonomic neuropathy
    B. Diabetic amyotrophy
    C. Acute painful neuropathy
    D. Symmetrical sensory neuropathy
    E. Diabetic mononeuropathy
13. Based on the UKPDS study, a 1% reduction in A1c results in the following except:
A. 14% drop in heart attacks
B. 17% drop in cerebrovascular accidents
C. 21% drop in diabetes-related deaths
D. 37% drop in microvascular complications
E. 43% drop in peripheral vascular disease

14. The following conditions warrant a less stringent A1c target of between 7.0–8.0% except:
A. Elderly folks living alone
B. End stage kidney failure
C. Episode of severe hypoglycaemia in the fasting month of Ramadan
D. History of hypoglycaemia in a patient with cardiovascular disease
E. Short life expectancy due to metastatic disease

15. Which of the following is FALSE about metformin therapy in diabetes mellitus?
A. It is best taken with or after meals and the dose increased weekly to its optimal dose.
B. Its dose should be halved in stage 3 chronic kidney disease with a GFR of between 45-60 ml/min/1.73 m².
C. It should be promptly stopped when a patient is completely switched to insulin therapy.
D. It is responsible in lowering fasting hyperglycaemia.
E. The optimal dose is between 1,500 to 2,000 mg daily.

16. All of the following are true of hypoglycaemia EXCEPT:
A. Frequency increases with the use of insulin and insulin secretagogues in an attempt to achieve tight glycaemic control
B. It may be associated with prolonged QT interval and ST segment depression on ECG
C. Patients who have a history of cardiovascular disease who develops hypoglycaemia should have their A1c target reevaluated.
D. Severe hypoglycaemia increases the likelihood of subsequent cardiovascular diseases
E. Stress hormone responses are augmented in nocturnal hypoglycaemia

17. The following pairing of side effects of special interest and their respective new anti-diabetic agents are true EXCEPT:
A. Bladder cancer - pioglitazone
B. Ketoacidosis - SGLT2 inhibitors
C. Myopathy – DPP-4 inhibitors
D. Osteoporosis - canagliflozin
E. Pancreatitis – glucagon-like peptide -1 receptor agonist

18. A sedentary 50-year-old lawyer with diabetes is found to have an A1c of 9.0% with a FBG of 8.8 mmol/l during his routine clinic follow-up. He is compliant to his treatment consisting of metformin 1 gm bid, gliclazide MR 90 mg daily and acarbose 50 mg tid. His BMI is 28 kg/m² and he does not complain of any hypoglycaemia. Which is your next course of action?
A. Counsel him to look after his diet and increase his physical activity (1.5 hour a week)
B. Increase his acarbose to 100 mg TID
C. Increase his gliclazide MR to 120 mg daily
D. Increase his metformin to 1 gm TID
E. Introduce basal insulin at 0.2 units/kg at bedtime
19. The insulin pen can be left in following places without adversely affecting the insulin content with the exception of:
A. in a locker of a classroom
B. in a parked car under a hot sun
C. in the pocket of one’s pants
D. on a working table in the office
E. on a dining table in the kitchen

20. An 82-kg middle aged obese housewife with diabetes has an A1c level of 10.0% with a FBG of 6.7 mmol/l and a pre-dinner blood glucose level of 8.8 mmol/l. She claims to be compliant to her therapy of mixed insulin 44 units BID and does not complain of any hypoglycaemia. She is busy in the morning looking after the welfare of her family that she sometimes misses breakfast.
Which of the following factors most likely contribute to the clinical scenario?
A. She does not look after her diet
B. She does not follow any exercise regime
C. Most probably she has a heavy lunch
D. Her compliance to insulin is suspect
E. She may resort to traditional medications

21. A 45-year-old business man is distraught at the death of his elder brother who died of a myocardial infarction. He himself has a history of diabetes, hypertension and dyslipidaemia and is currently on metformin 1gm bid, gliclazide 80 mg bid, atorvastatin 10 mg and perindopril 4 mg daily. His BP is 150/92 mmHg with a BMI of 28 kg/m². His results are as: A1c 10.8%, FBG 8.8 mmol/L, LDL 3.0 mmol/l with + protein on urinalysis.
In addition to increasing his atorvastatin and perindopril, what other measure will you take?
A. Add either a DPP-4 or SGLT2 inhibitors.
B. Encourage him to exercise and control his diet
C. Initiate basal insulin at bedtime and titrate accordingly
D. Prescribe 100 mg of aspirin after his dinner
E. Refer him to the cardiologist for stress test and coronary angiogram

22. The following patients are at high risk of endangering themselves if they were to fast in Ramadan with the exception of:
A. Those with A1c > 10 % and FBG > 13 mmol/l
B. History of recent hospital admission for hypoglycaemia
C. History of repeated admissions for diabetic ketoacidosis
D. Obese patients on high doses of insulin
E. Type 1 DM who is loosing weight

23. The following statements regarding oral Glucose Tolerance Test (OGTT) in pregnancy are true with the exception of:
A. A 25-year-old primigravida with no risk factors for GDM does not warrant any screening.
B. Those with risk factors for developing GDM should be screened at booking.
C. Those with risk factors for developing GDM whose initial OGTT were normal should be screened 4-6 weeks later.
D. Those with risk factors for developing GDM whose repeat OGTT before 24 weeks were normal (twice OGTT normal) should have another OGTT at 24-28 weeks of gestation.
E. Those with no risk factors for GDM but has a history of macrosomia should be screened at booking.
24. With regards to the management of hyperglycaemia in pregnancy, the following are true EXCEPT:
A. A trial of diet and lifestyle modification should be instituted in the first two weeks following the diagnosis of GDM, failing which insulin should be introduced.
B. Metformin may be continued in patients with polycystic ovarian syndrome who become pregnant.
C. In patients with type 2 DM, glibenclamide may be continued if pre-natal A1c was <6.5%.
D. Once a day morning basal insulin is a suitable alternative to three times bolus insulin when initiating insulin therapy.
E. Based on Cochrane Reviews and health technology assessments, insulin analogues are no more efficacious than human insulins except in reducing nocturnal hypoglycaemia.

25. The following misconceptions about diabetes management are false except:
A. Strict glycaemic control does not improve the risk of developing cardiovascular disease
B. Weight gain is an inevitable consequence of lowering blood glucose levels
C. Stress hyperglycaemia is associated with worse clinical outcome than hyperglycaemia of diabetes.
D. Newer oral anti-diabetic agents are more efficacious than older oral anti-diabetic agents
E. Insulin analogues are more effective than human insulins in controlling blood glucose levels
<table>
<thead>
<tr>
<th>Question No.</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question No.</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>D</td>
</tr>
<tr>
<td>13</td>
<td>B</td>
</tr>
<tr>
<td>14</td>
<td>C</td>
</tr>
<tr>
<td>15</td>
<td>C</td>
</tr>
<tr>
<td>16</td>
<td>E</td>
</tr>
<tr>
<td>17</td>
<td>E</td>
</tr>
<tr>
<td>18</td>
<td>E</td>
</tr>
<tr>
<td>19</td>
<td>B</td>
</tr>
<tr>
<td>20</td>
<td>C</td>
</tr>
<tr>
<td>21</td>
<td>C</td>
</tr>
<tr>
<td>22</td>
<td>D</td>
</tr>
<tr>
<td>23</td>
<td>A</td>
</tr>
<tr>
<td>24</td>
<td>C</td>
</tr>
<tr>
<td>25</td>
<td>C</td>
</tr>
</tbody>
</table>
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION