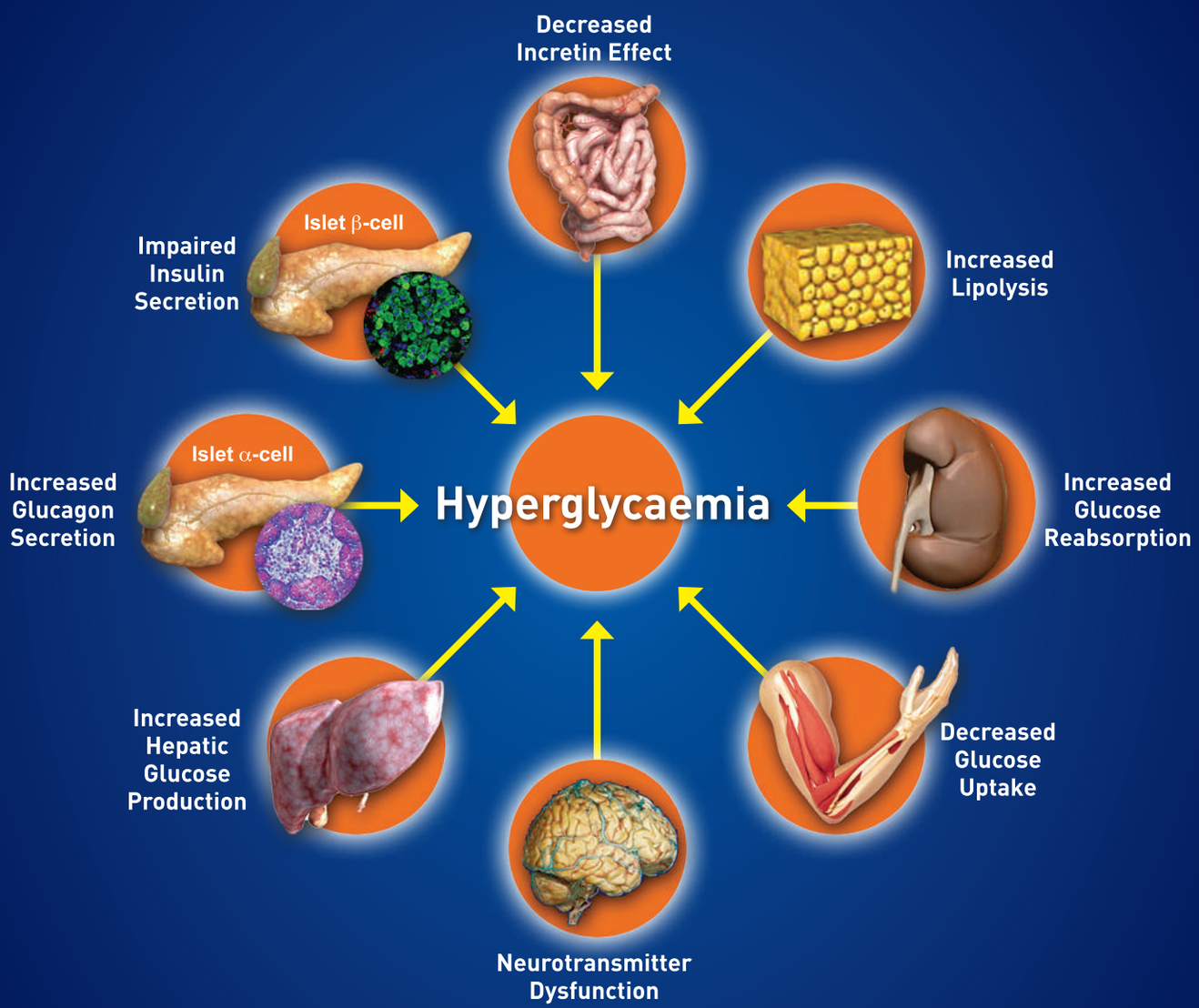
2016

MOH/P/PAK/303.15 (GU)

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

5TH EDITION



MALAYSIAN ENDOCRINE & METABOLIC SOCIETY

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

DIABETES MALAYSIA

FAMILY MEDICINE SPECIALISTS ASSOCIATION OF MALAYSIA

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 GLIP-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.

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PREFACE

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 secretagoues 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 outperformed 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

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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

No.	Topic	Duration (minutes)	
		Lecture	Case Studies
1.	Overview of Type 2 Diabetes Mellitus & Revised CPG for the Management of T2DM 2015		
2.	Screening & Diagnosis		
3.	Target for Control		
4.	Medical Nutrition Therapy & Low Glycaemic Index Diet		
5.	Physical Activity		
6.	Oral Anti-Diabetic Medications		
7.	Insulin Therapy & Injectables		
8.	Diabetes with Hypertension		
9.	Diabetes with Dyslipidaemia		
10.	Diabetes with Obesity		
11.	Management of Diabetic Emergencies - Hypoglycaemia		
12.	Management of Diabetic Emergencies – DKA & HHS		
13.	Management of Chronic Complications 1		
14.	Management of Chronic Complications 2		
15.	Diabetes in Pregnancy		
16.	Diabetes in Ramadan		
17.	Diabetes in Adolescents		
18.	Prevention of Type 2 Diabetes Mellitus		
Total			

TOPIC

1

Lecture Notes

overview of type 2 diabetes mellitus & revise cpg for the management of T2DM 2015

SLIDE 1

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

SLIDE 2

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.

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

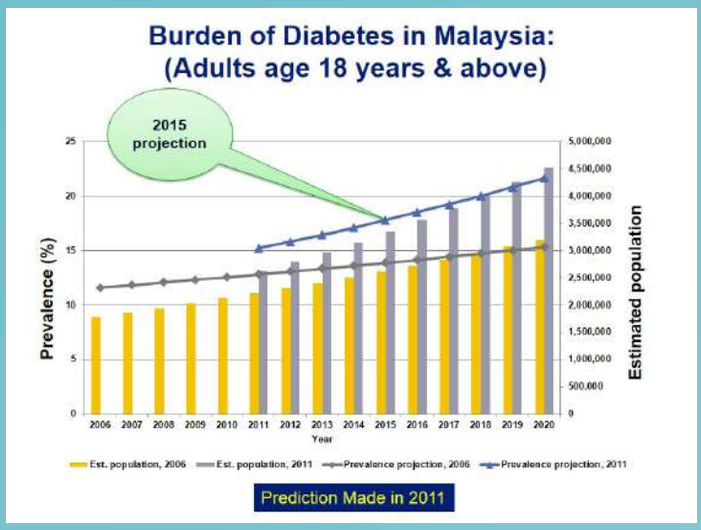
SLIDE 3

Diabetes: The Burden

- The prevalence of T2DM is increasing in the young with 5.5% (mostly undiagnosed) of those between ages 18-19 years affected by it.
- In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycaemic targets.
- Up to 25.1% of T2DM patients in the general population were on insulin compared to 65.4% in tertiary institutions.

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

SLIDE 4



SLIDE 5

Status of Diabetes Mellitus in Malaysia in the past 20 years

	2006 NHMS III	2011 NHMS IV	2015 NHMS V	2009 MSSM
Remarks	18 yrs old & above	18 yrs old & above	18 yrs old & above	18 yrs old & above
Prevalence	11.6%	15.2 %	17.5%	22%
Known diabetes	7.0%	8.2 %	8.3%	11 %
Undiagnosed diabetes	4.5%	7.0 %	9.2%	11%
Impaired Glucose Tolerance (IGT) / Fasting Glucose (IFG)	4.2%**	4.9 % based on IFG	4.7%	20.5% based on IGT

Use of fasting capillary finger prick BG

SLIDE 6

Prevalence of Risk Factors In Malaysia (1996-2015)

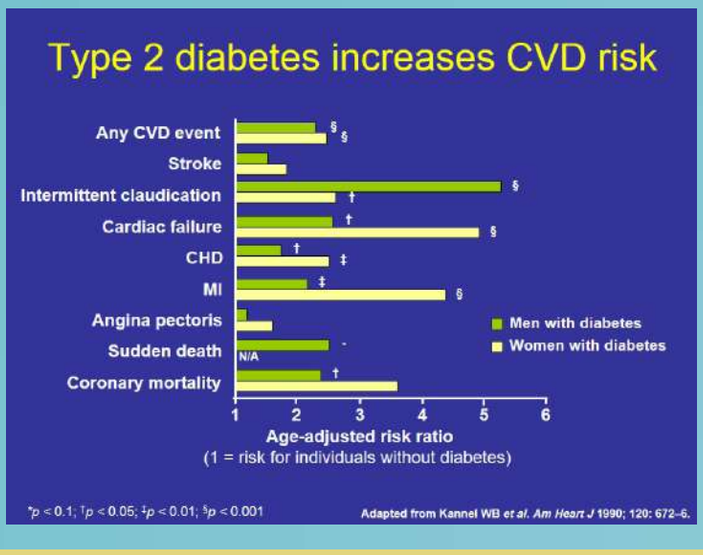
	NHMS II (1996)	NHMS III (2006)	NHMS IV (2011)	NHMS V (2015)
Age Group	≥18 yrs	≥ 18yrs	≥ 18yrs	≥ 18yrs
Smoking	24.8%	21.5%		22.8%
Physically inactive	88.4%	43.7%		33.5%
Unhealthy Diet	N.A.	N.A.		
Overweight (BMI ≥ 25 & < 30kg/m^2)	16.6%	29.1%		30.0% (WHO) 33.4% (M'sian CPG)
Obesity (BMI ≥30kg/m^2)	4.4%	14.0%		17.7% (WHO) 30.6% (M'sian CPG)

Body Mass Index (BMI) was classified using two guidelines; the Malaysian Clinical Practice Guidelines of Obesity (2004) and World Health Organization (1998).

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

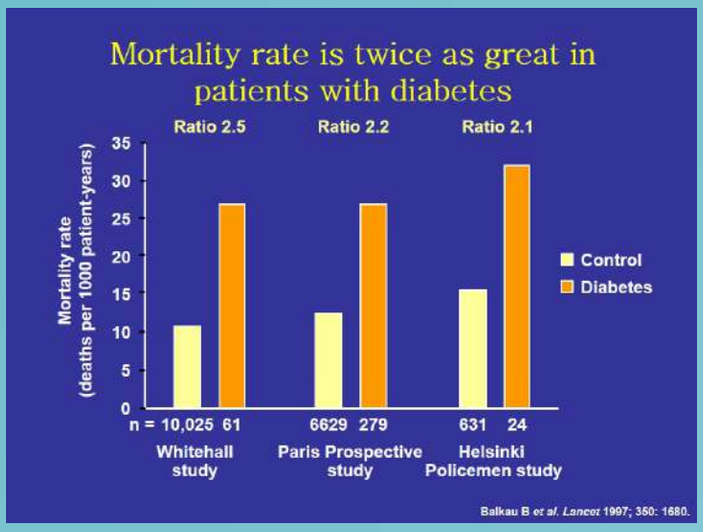


People with type 2 diabetes have a higher risk of CVD events relative to people without diabetes.

- 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.

Kannel WB *et al*. *Am Heart J* 1990; 120: 672–6.

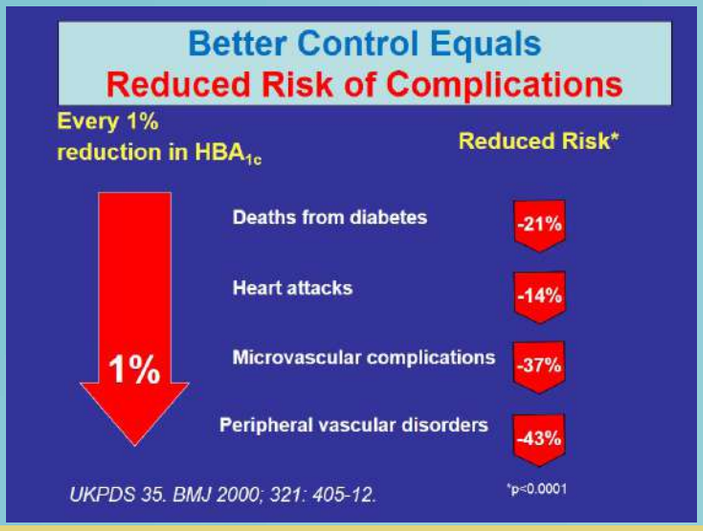
SLIDE 8



- 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.

Balkau B *et al*. *Lancet* 1997; 350: 1680.

SLIDE 9



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.

Stratton MI Adler AI, Neil AW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.

SLIDE 10

NDR – Patients registered
(Active patients; as of 27 August 2012)

States	Returns	Coverage of registration (Active patients) NDR	% Coverage
Johor	81,013	87,001	107.4
Kedah	77,931	37,114	47.6
Kelantan	24,774	26,102	105.4
Melaka	31,427	36,446	116.0
Negeri Sembilan	39,393	40,890	103.8
Pahang	43,871	38,215	87.1
Perak	68,372	65,336	95.6
Perlis	10,338	11,368	110.0
Pulau Pinang	31,895	37,942	119.0
Sabah	9,205	10,956	119.0
Sarawak	64,848	45,902	70.8
Selangor	104,137	91,965	88.3
Terengganu	16,944	18,585	109.7
WP Kuala Lumpur	23,728	28,901	121.8
WP Labuan	535	815	152.3
Malaysia	**628,411**	**577,538**	**91.9**

SLIDE 11

Diabetes Clinical Audit (2012)

Variable	Targets	Total no. of tests	Meeting target (%)	Mean	95% CI
HbA1c	< 6.5 %	99,823	23.7	8.1	8.1 - 8.1
BP : Systolic	< 130 mmHg	121,751	47.6	135.5	135.4 - 135.6
BP: Diastolic	< 80 mmHg	121,726	67.2	78.4	78.3 - 78.4
Blood pressure	< 130 / 80 mmHg	121,698	40.9		
Total cholesterol	< 4.5 mmol/l	101,286	28.5	5.2	5.2 - 5.2
TG	≤ 1.7 mmol/l	101,008	60.6	1.8	1.8 - 1.8
HDL	≥ 1.1 mmol/l	76,214	65.5	1.3	1.3 - 1.3
LDL	≤ 2.6 mmol/l	75,734	37.8	3.1	3.1 - 3.1
BMI	< 23 kg/m2	108,559	16.6	27.4	27.3 - 27.4
Waist circumference	< 90 cm (Male)	35,520	33.6	94.0	93.9 - 94.1
	< 80 cm (Female)	55,493	14.4	90.7	90.6 - 90.8
Total: 130,340 Patients					

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Diabetes Clinical Audit (2009-2012)

Anti-Diabetics	2009	2010	2011	2012
Metformin	81.7%	85.7%	82.3%	82.2%
Sulphonylureas	65.2%	62.9%	59.5%	56.6%
Alpha-glucosidase inhibitors	4.7%	5.9%	6.5%	4.8%
Insulin	**12.0%**	**11.9%**	**17.1%**	**21.3%**
Monotherapy (OHA)	33.6%	34.1%	27.8%	27.3%
>= 2 OHA	51.1%	51.7%	48.7%	45.5%
OHA + insulin	**8.8%**	**8.9%**	**13.2%**	**16.2%**
Diet only	3.4%	2.3%	6.4%	5.9%

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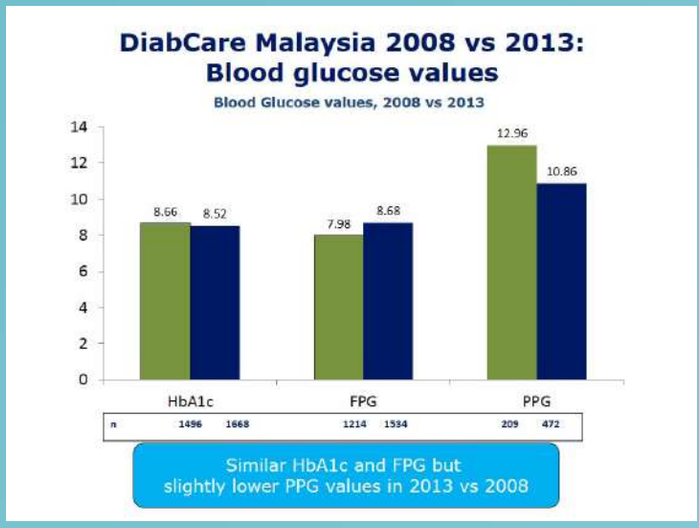
SLIDE 13

DiabCare Malaysia 2008 vs 2013: Blood glucose values

ADA		AACE, IDF	
2008	2013	2008	2013
HbA1c >7% (%)		HbA1c ≥6.5% (%)	
71.9	**76.3**	85	**87.3**
FPG >7.2 mmol/L (%)		FPG ≥ 6.1 mmol/L (%)	
39.6	**48.6**	54.4	**66.6**

~ ¾ of patients were above ADA targets for HbA1c

SLIDE 14



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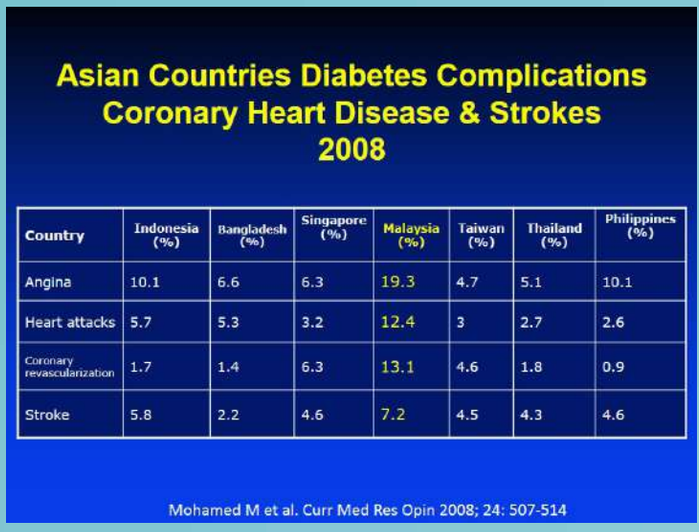
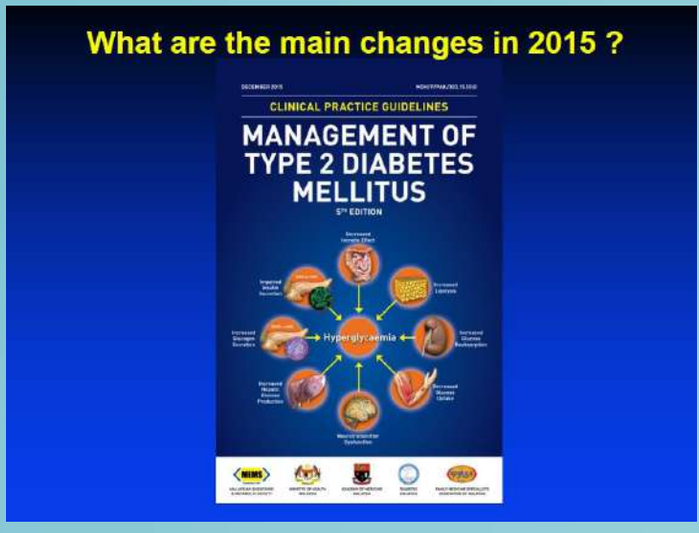


Country	Indonesia (%)	Bangladesh (%)	Singapore (%)	Malaysia (%)	Taiwan (%)	Thailand (%)	Philippines (%)
Angina	10.1	6.6	6.3	19.3	4.7	5.1	10.1
Heart attacks	5.7	5.3	3.2	12.4	3	2.7	2.6
Coronary revascularization	1.7	1.4	6.3	13.1	4.6	1.8	0.9
Stroke	5.8	2.2	4.6	7.2	4.5	4.3	4.6

SLIDE 16



SLIDE 17

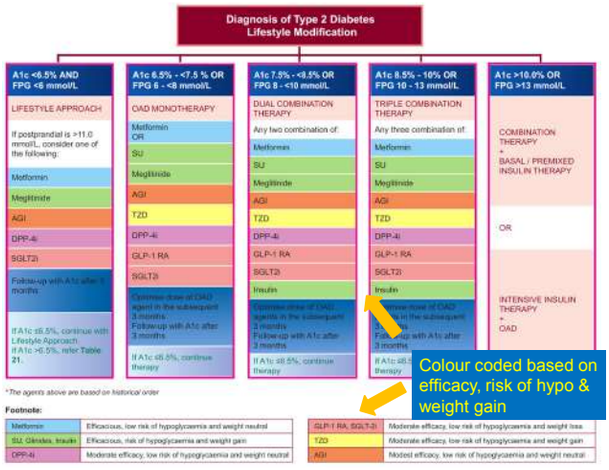
What are the (10) main changes in 2015 ?

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, DKA, HHS
   e) Mx 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 cardiological work-up (DAID Study)
9. Primary prevention with aspirin only in those above 65 years old (JPAD Study).
10. Hyperglycaemia in Pregnancy (GDM &T2DM)

For the first time CPG was revised without involvement of pharmaceutical companies

SLIDE 18

Algorithm 5: Treatment Algorithm for Newly Diagnosed T2DM



SLIDE 19

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

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

MDI = Multiple daily injections; [1] Intensify involve changing the regimen; SU = sulphonylureas

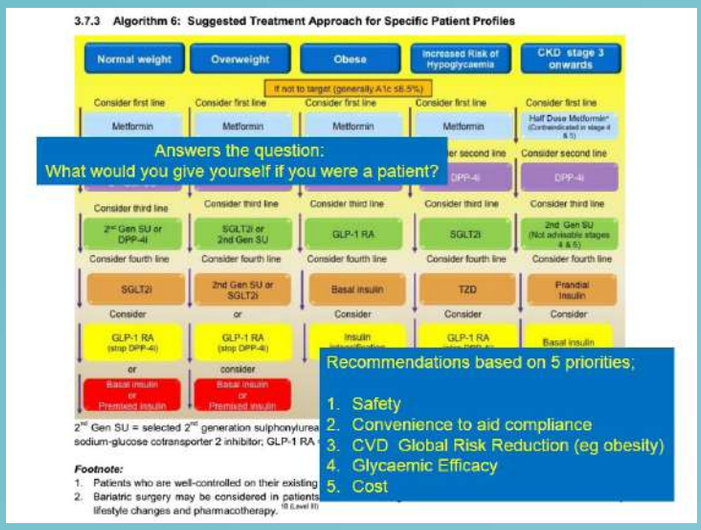
Box 1: Selection of Anti-diabetic Agents

SU
Meglitinide
AGI
TZD
DPP-4i
GLP-1 RA
SGLT2i

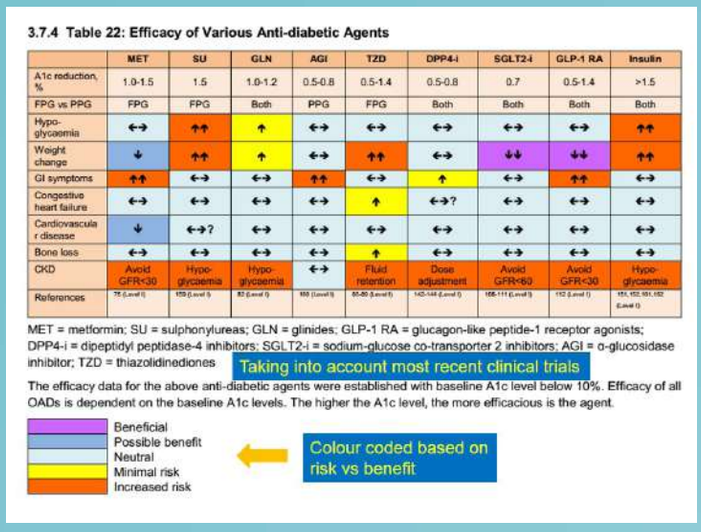
Colour coded based on efficacy, risk of hypo & weight gain

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

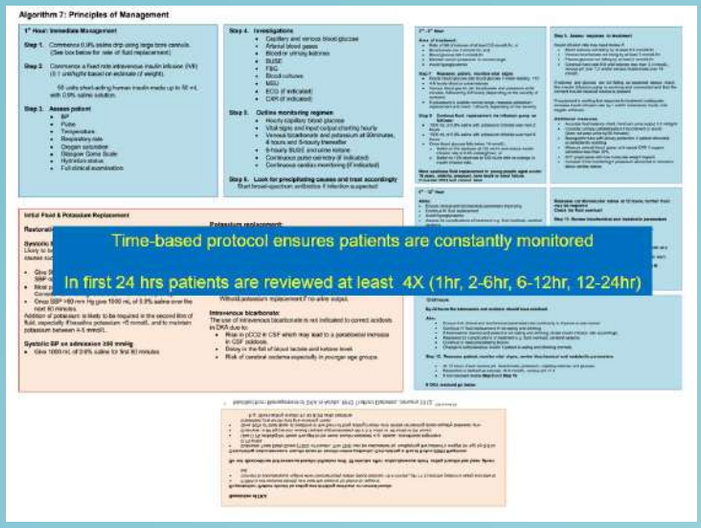
SLIDE 20



SLIDE 21

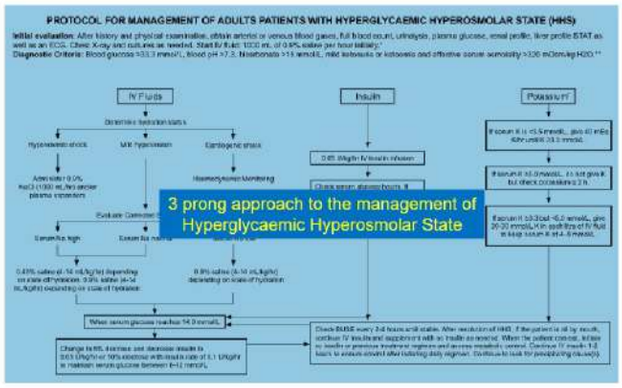


SLIDE 22



SLIDE 23

Algorithm 8: Management of T2DM with Hyperglycaemic Hyperosmolar State



*Modified from Umpierrez GE, Murphy MB, Kitabchi AE. Diabetic Ketoacidosis and Hyperglycaemic Hyperosmolar Syndrome. Diabetes Spectrum, 2002. [252 (Level II-2)]

** Effective serum osmolality calculation: SI units: $2Na^+ + 2K^+$ + Glucose + Urea (all in mmol/L)

*** Serum Na^+ should be corrected for hyperglycaemia (SI units: Corrected serum sodium = Measured serum sodium + [(Glucose measured - 5.6)/5.6] x 2.4; 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

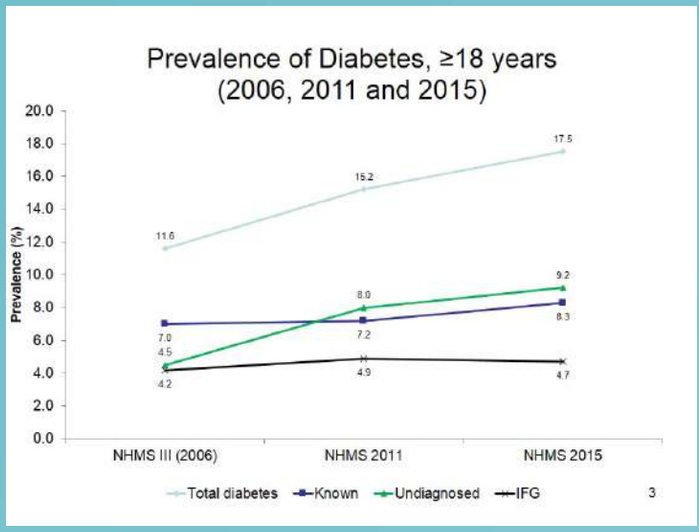
TOPIC

2

Lecture Notes

screening and diagnosis

SLIDE 1



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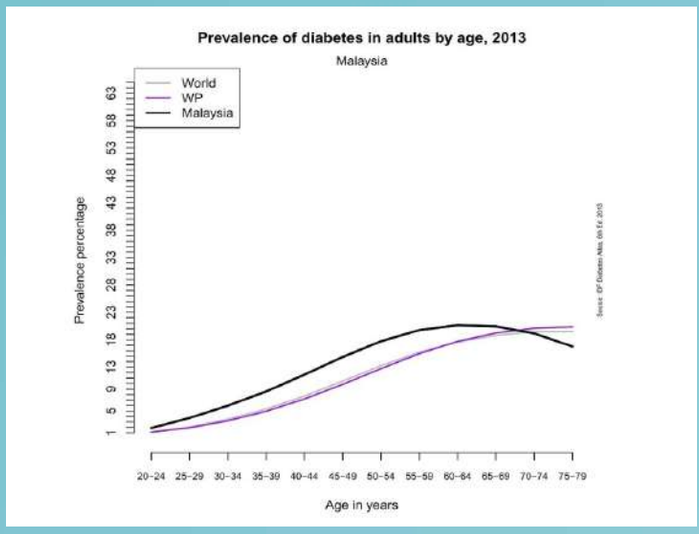

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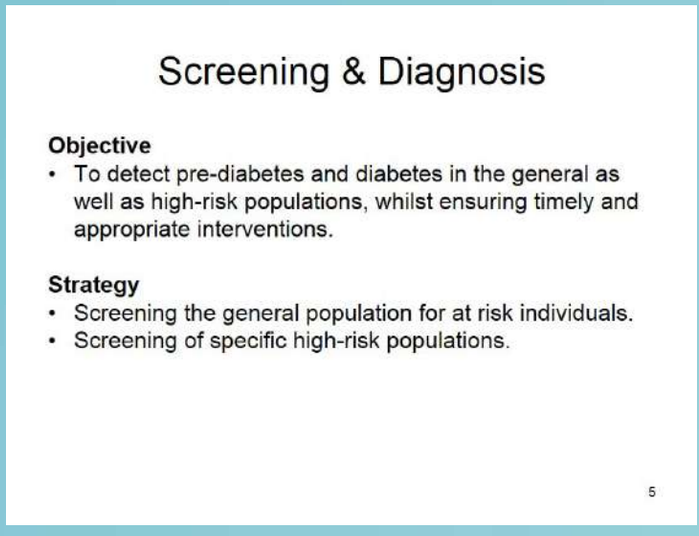


SLIDE 4

Who should be screened?

Symptomatic Individuals

6

SLIDE 5

Symptoms & Signs

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

SLIDE 6

Who should be screened?: Asymptomatic

- Screening should begin at age ≥ 30 years.

8

SLIDE 7

Who should be screened? Asymptomatic

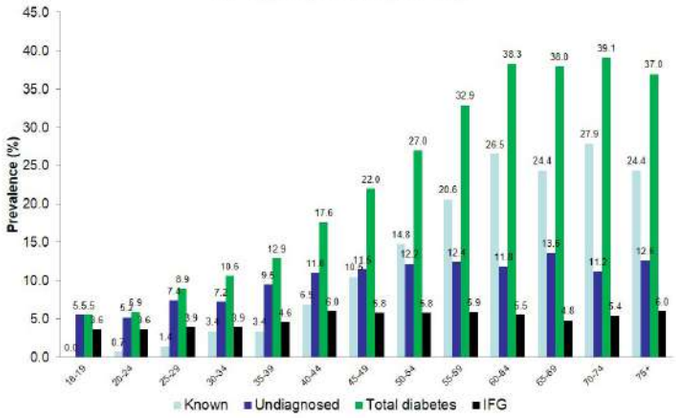
- Adults who are overweight or obese (by BMI or waist circumference), **and** have one or more of the following additional risk factors:
  - First degree relative with diabetes
  - History of CVD
  - Hypertension
  - IGT or IFG
  - Abnormal HDL or TG
  - Other clinical conditions associated with insulin 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.

9

SLIDE 8

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



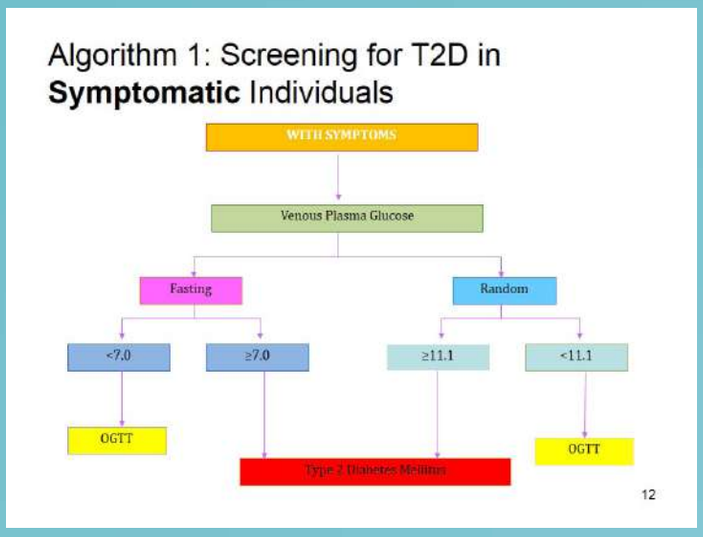
SLIDE 9

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.

11

SLIDE 10



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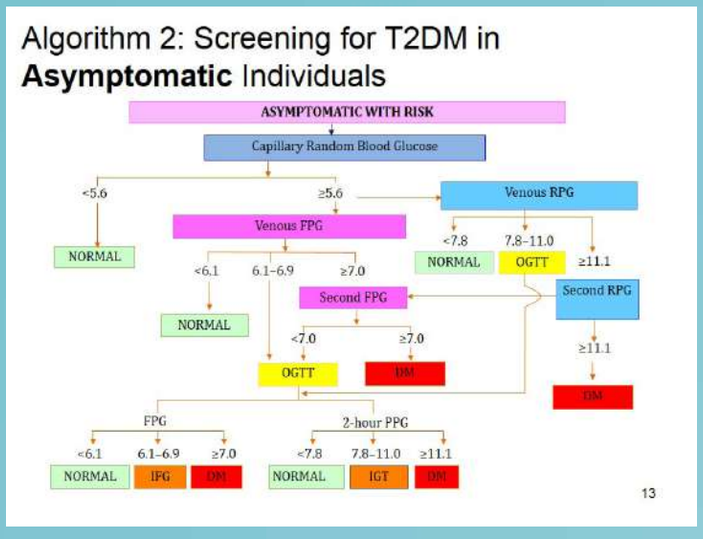
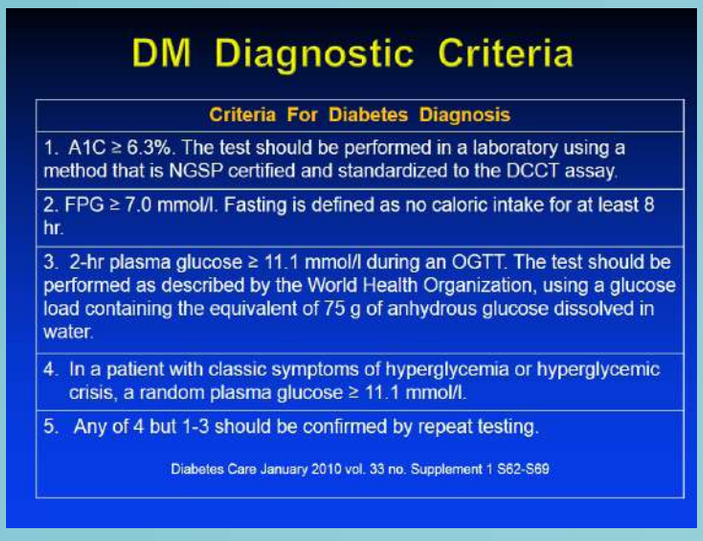


SLIDE 12



SLIDE 13

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

4. A1c Level of ≥ 6.3 % (CPG T2DM 2015).

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

SLIDE 14

Diagnostic values – A1c

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

- 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.

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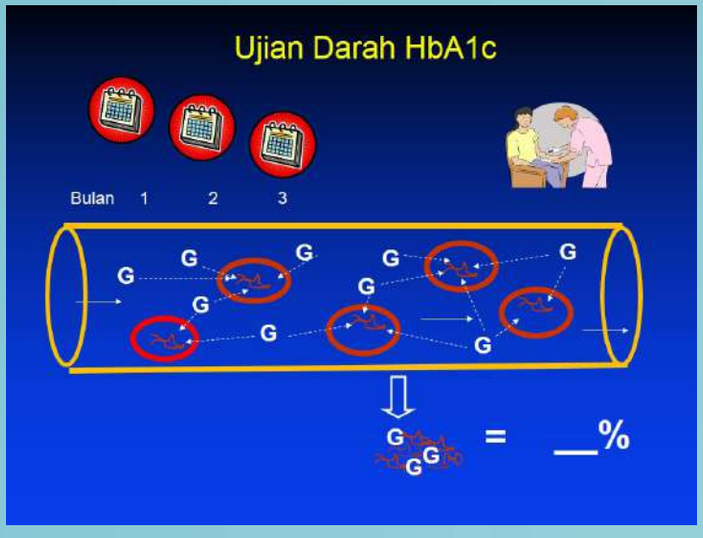
SLIDE 15



SLIDE 16

New A1c Cut-Off level to diagnose T2DM in Malaysians

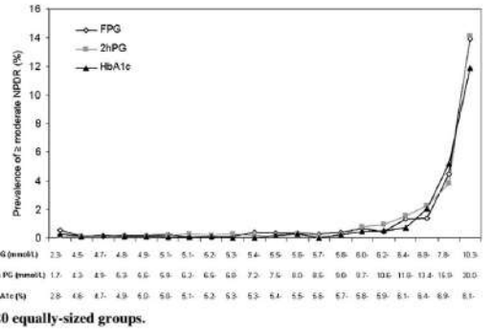
Research: Epidemiology

Prevalence of diabetes in Malaysia and usefulness of HbA_{1c} as a diagnostic criterion

A1c of 6.3% has a specificity of 97% in diagnosing diabetes based MSSM 2008.
Individuals with A1c between 5.6% and 6.2% are labeled as pre-diabetes.

SLIDE 17

Figure 1. Prevalence of diabetes-specific retinopathy (≥ moderate non proliferative retinopathy) by vigintiles* of distribution of FPG, 2-h PG and HbA1c from DETECT-2.



*20 equally-sized groups.

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus
Abbreviated Report of a WHO Consultation 2011.

SLIDE 18

Recognize pitfalls of A1C: conditions that can affect value

Factors affecting A1C	Increased A1C
Erythropoiesis	B12/Fe deficiency Decreased erythropoiesis
Altered hemoglobin	
Altered glycation	Chronic renal failure ↓↓erythrocyte pH
Erythrocyte destruction	Splenectomy
Assays	Hyperbilirubinemia Carbamylated Hb ETOH Chronic opiates

While A1c is an excellent measure for diagnosis, it is essential to know conditions where the value may not adequate 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 turn over states and factors that increase erthropoeisis 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.

SLIDE 19

Pros and Cons of Diagnostic Tests

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

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

SLIDE 20

Advantages and disadvantage of assays for glucose and HbA1c

	Glucose	HbA1c
Patient preparation prior to collection of blood	Stringent requirements if measured for diagnostic purposes.	None.
Processing of blood	Stringent requirements for rapid processing, separation and storage of plasma or serum minimally at 4 °C.	Avoid conditions for more than 12hr at temperatures >23C. Otherwise keep at 4C (stability minimally 1 week).
Measurement	Widely available	Not readily available world-wide
Standardization	Standardized to reference method procedures.	Standardized to reference method procedures.
Routine calibration	Adequate.	Adequate.
Interferences: illness	Severe illness may increase glucose concentration.	Severe illness may shorten red-cell life and artifactually reduce HbA1c values.
Haemoglobinopathies	Little problem unless the patient is ill.	May interfere with measurement in some assays.
Haemoglobinopathy traits	No problems.	Most assays are not affected.
Affordability	Affordable in most low and middle income country settings.	Unaffordable in most low and middle-income country settings.

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus
Abbreviated Report of a WHO Consultation 2011.

SLIDE 21

Advantages and disadvantages of various HbA1c assay methods

Assay	Principle	Advantages	Disadvantages
Ion Exchange Chromatography	HbA1c has lower isoelectric point and migrates faster than other Hb components.	Can inspect chromograms for Hb variants. Measurements with great precision.	Variable interference from hemoglobinopathies, HbF and carbamylated Hb but the current ion exchange assays correct for HbF and carbamylated Hb does not interfere.
Boronate Affinity	Glucose binds to m-aminophenylboronic acid.	Minimal interference from haemoglobinopathies, HbF and carbamylated Hb.	Measures not only glycation of N-terminal valine on β chain, but also β chains glycated at other sites and glycated α chains.
Immunoassays	Antibody binds to glucose and between 4-10 N-terminal amino acids on β chain.	Not affected by HbE, HbD or carbamylated Hb Relatively easy to implement under many different formats.	May be affected by haemoglobinopathies with altered amino acids on binding sites. Some interference with HbF.

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus
Abbreviated Report of a WHO Consultation 2011.

SLIDE 22

Method	Interference from HbC	Interference from HbS	Interference from HbE	Interference from HbD	Interference from elevated HbF
Arkray ADAMS A1c HA-8180V (Menarini)	No	No	HbA1c not quantified	HbA1c not quantified	No <30% HbF
Axis-Shield Afinion	No	No	No	No	$
Beckman AU system	Yes	Yes	No	No	$
Beckman Synchron System	No	No	No	No	$
Bio-Rad D-10 (A1c program)	No	No	No	No	No <10% HbF
Bio-Rad Variant II NU	-	-	No	No	No <10% HbF
Bio-Rad Variant II Turbo	No	No	Yes	Yes	No <5% HbF
Bio-Rad Variant II Turbo 2.0	No	No	No/Yes (conflicting reports)	No	No <25% HbF
Bio-Rad in2it	Yes	No	Yes	No	$
Ortho-Clinical Vitros	No	No	No	No	$
Polymer Tech Systems A1cNOW	Yes	Yes	No	No	$
Roche Cobas Integra Gen.2	No	No	No	No	$
Roche/Hitachi (Tina Quant II)	No	No	No	No	$
Sebia Capillarys 2 Flex Piercing	No	No	No	No	No <15% HbF
Siemans Advia A1c (new version)	No	No	@	@	$
Siemens DCA 2000/Vantage	No	No	No	No	No <10% HbF
Siemens Dimension	No	No	No	No	$
Tosoh G7	Yes	No	Yes	No	No <30% HbF
Tosoh G8	No	No	Yes	No	No ≤30% HbF
Trinity (Primus) HPLC (affinity)	No	No	No	No	No <15% HbF

@ In the absence of specific method data, it can generally be assumed that immunoassay methods do not have clinically significant interference from HbE and HbD because the E and D substitution are distant from the N-terminus of the hemoglobin beta chain
$ In the absence of specific method data, it can generally be assumed that both immunoassay and boronate affinity methods show interference from HbF levels above ~ 10-15%

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.

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SLIDE 24

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 ≥6.1 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.

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TOPIC

2

Case Study

screening and diagnosis

SLIDE 1

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/m^2, 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

SLIDE 4

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)

SLIDE 5

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 AIC comes back as 6.3%.

SLIDE 6

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.

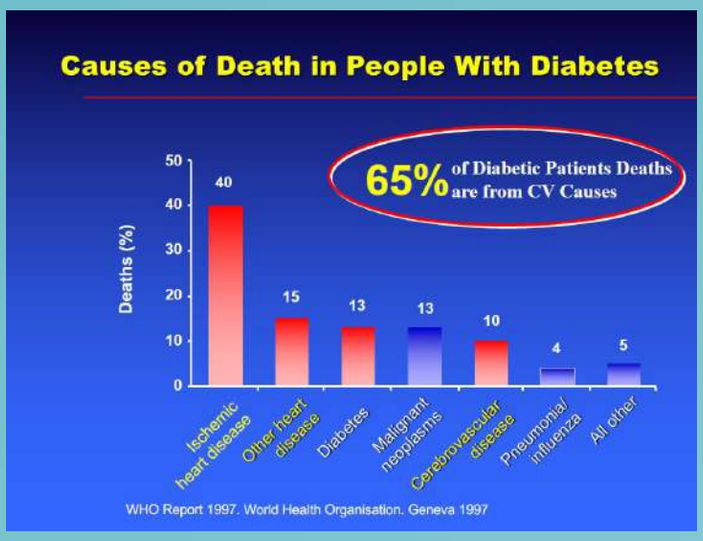
TOPIC

3

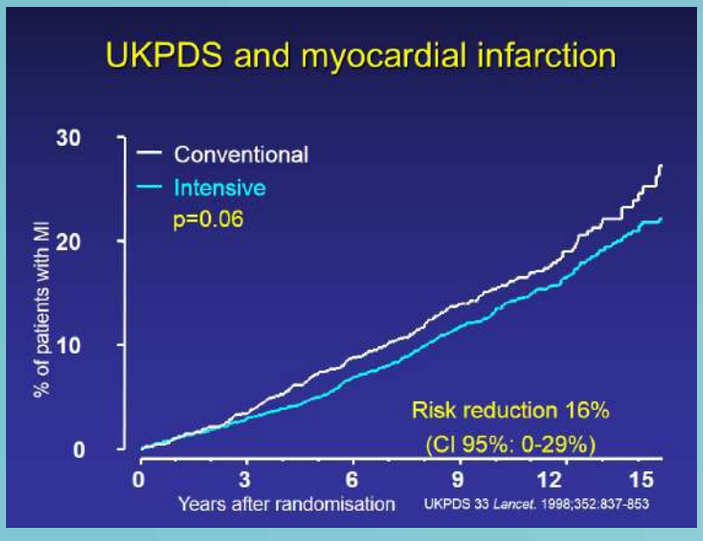
Lecture Notes

targets for control

SLIDE 1



SLIDE 2



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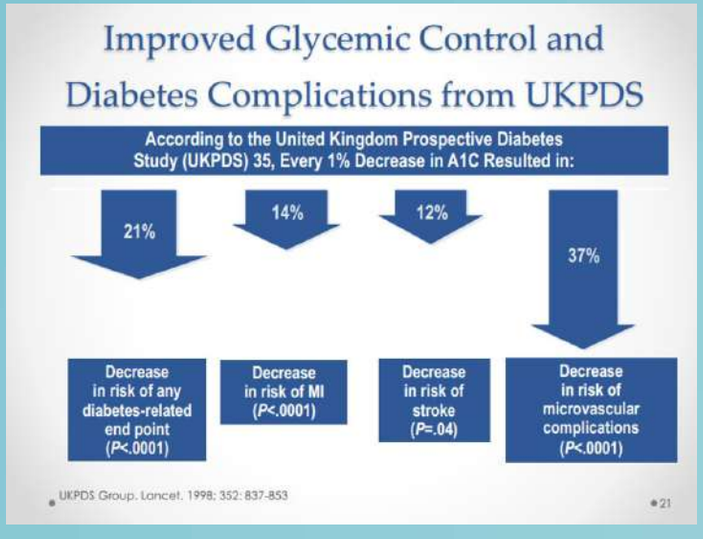

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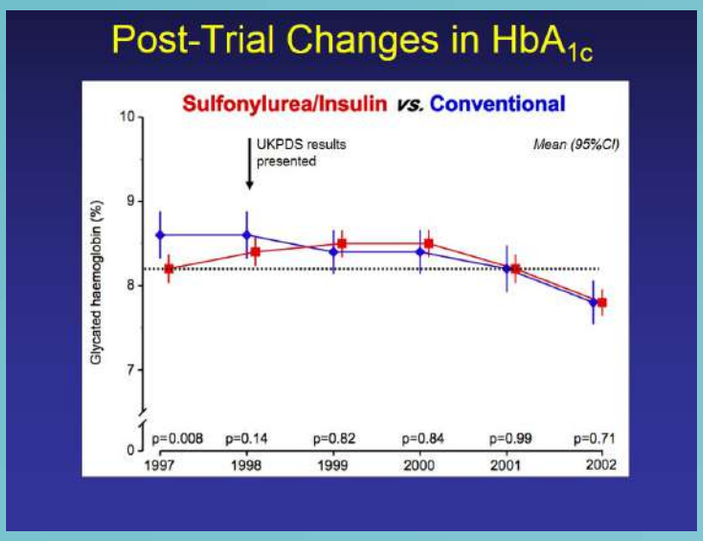

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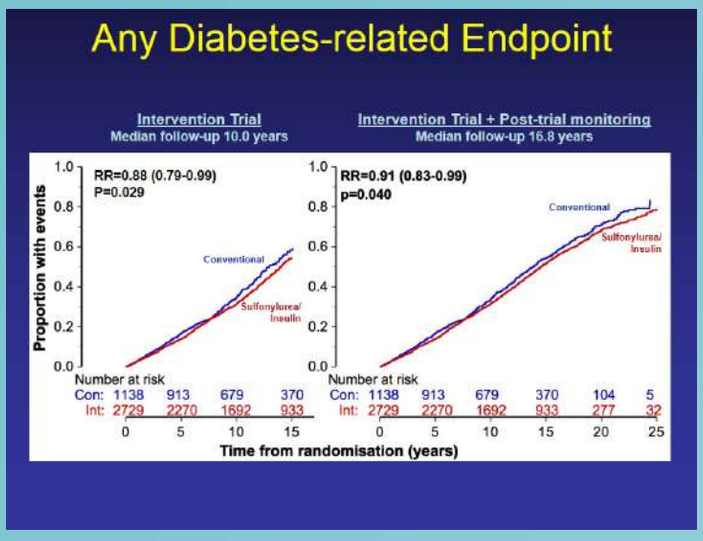

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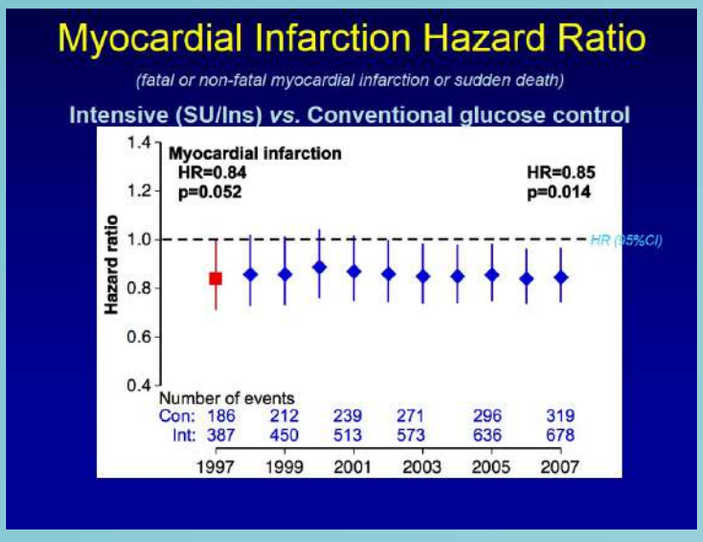

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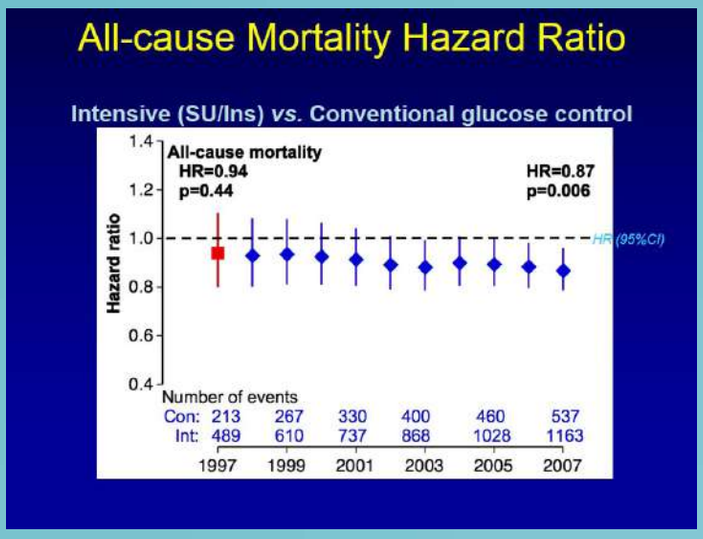

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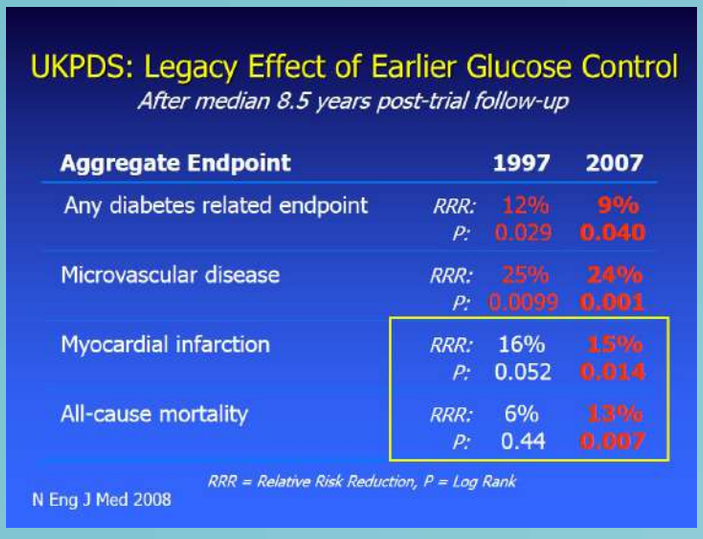
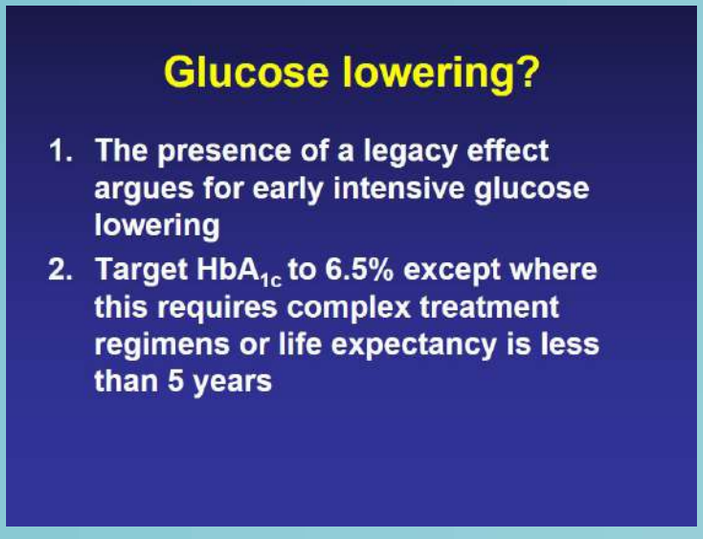


SLIDE 9



SLIDE 10

Questions addressed in RCT of Type 2 diabetes treatment

Question 1:

Does treatment-directed lowering HbA1c (below 6.0 to 6.5%) reduce CV endpoints

UKPDS [P]

UKPDS [P] Long-term follow-up

ACCORD [P, S]

ADVANCE [P, S]

VADT [P, S]

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.

N Engl J Med 2015 Jun 4; 372: 2197-2206.

P, primary prevention; S, secondary prevention

SLIDE 11

Early vs Late Glycemic Intervention

	UKPDS[a] (*N*=3867)	ADVANCE[b] (*N*=11,140)	ACCORD[c] (*N*=10,251)	VADT[d] (*N*=1791)
	Disease progression →			
Duration of diabetes, y	0*	8	10	11.5
Mean age, y	53	66	62	60
Mean baseline HbA_{1c}, %	7.1	7.5	8.3	9.4
Mean baseline FPG, mmol/L	8.0	8.5	9.7	11.4
ΔHbA_{1c}, %	**0.9**	**0.7**	**1.1**	**1.5**
CVD	↔ ↓	↔	↔	↔ ↓
Mortality	↔ ↓	↔	↑	↔

*Newly diagnosed patients with no previous history of CVD.

a. UKPDS Group. *Lancet*. 1998;352:837-853.[1]
b. ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.[2]
c. ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.[3]
d. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.[4]

SLIDE 12

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

Study	Diabetes Duration (mean)	Antihyperglycemic Medication[a]	Follow-up (median)	A_{1c}: Baseline, Between-arm Difference	Microvascular	CVD	Mortality
ADVANCE[3]	8 years	Intensive glucose control including gliclazide vs standard treatment	5 years	7.5% (both arms)[b], –0.8%[d]	↓	↔	↔
ACCORD[4,5]	10 years	Multiple drugs in both arms	3.4 years	8.1% (both arms)[c], –1.1%[c]	↓	↔	↑
VADT[6]	11.5 years	Multiple drugs in both arms	5.6 years	9.4% (both arms)[b], –1.5%[d]	↔	↔	↔

[a]Median between-arm difference; [b]Mean between-arm difference; [c]Median baseline HbA_{1c}.
CV = cardiovascular; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ACCORD = Action to Control Cardiovascular Risk in Diabetes; VADT = Veterans Affairs Diabetes Trial. 2. Holman RR et al. *N Engl J Med*. 2008;359:1577–1589. 3. ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358:2560–2572. 4. Gerstein HC et al. *N Engl J Med*. 2008;358:2545–2559. 5. Ismail-Beigi F et al. *Lancet*. 2010;376:419–430. 6. Duckworth W et al. *N Engl J Med*. 2009;360:129–139.

13

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) was a study of 11,140 patients randomized to receive intensive glucose control (HbA_{1c} target ≤6.5%) with addition of gliclazide (or substitution of

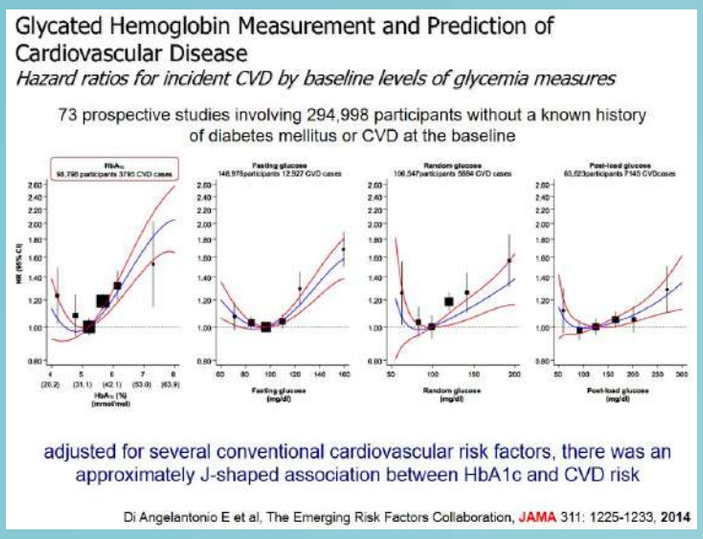
gliclazide for other sulfonylurea therapy) or standard glucose control (HbA_{1c} target defined by local guidelines).

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 HbA_{1c} 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 HbA_{1c} <6%) vs standard therapy (target HbA_{1c} 7.0–7.9%). An absolute between-treatment difference in HbA_{1c} 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]

SLIDE 13



SLIDE 14

A1c Targets

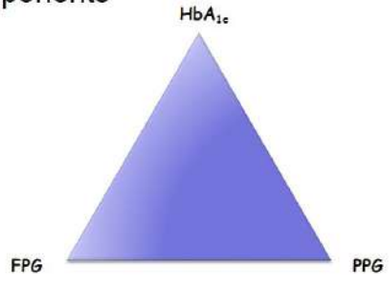
Individualised A1c Targets and Patients' Profile		
Tight (6.0 – 6.5%)	6.6 – 7.0%	Less tight (7.1 – 8.0%)
• Newly diagnosed • Younger age • Healthier •(long life expectancy, no CVD complications) • Low risk of hypoglycaemia	• All others	• Comorbidities (coronary artery disease, heart failure, renal failure,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

15

SLIDE 15

Treatment Strategies: Glucose Triad

- Treatment strategy should target all 3 components



Ceriello A, Colagiuri S. Diabet Med. 2008;25(10):1151-1156.

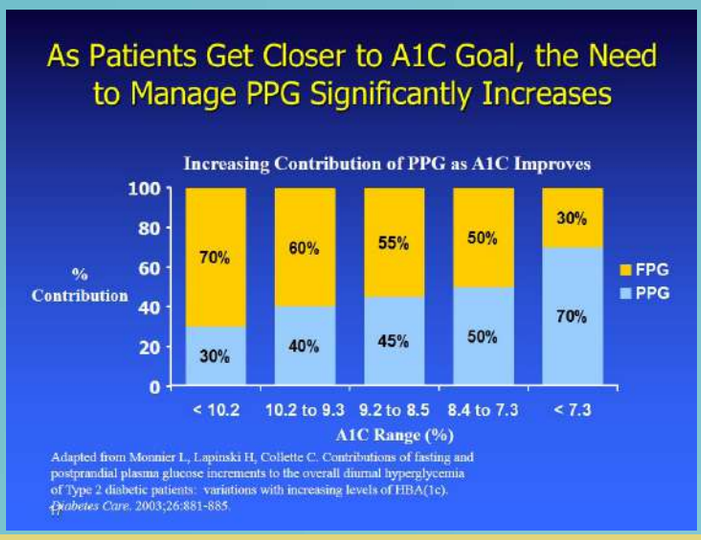
Main Point: Highlight the importance of a therapy that addresses this glucose triad, even at insulin initiation.

As FPG and postprandial plasma glucose (PPG) contribute to varying degrees at differing HbA_{1c} 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 HbA_{1c}, which has been clearly associated with lowering risks of future complications.

Reference:

Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabet Med.* 2008;25(10):1151-1156.

SLIDE 16

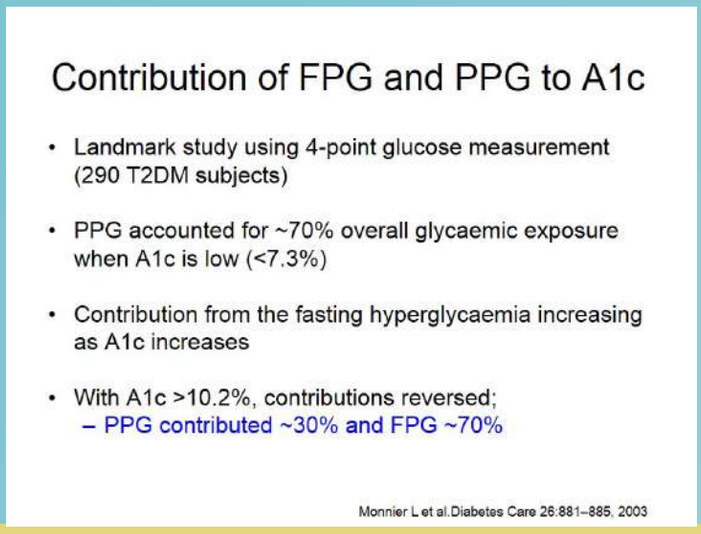


As Patients Get Closer to A1C Goal, the Need to Successfully Manage PPG Significantly Increases

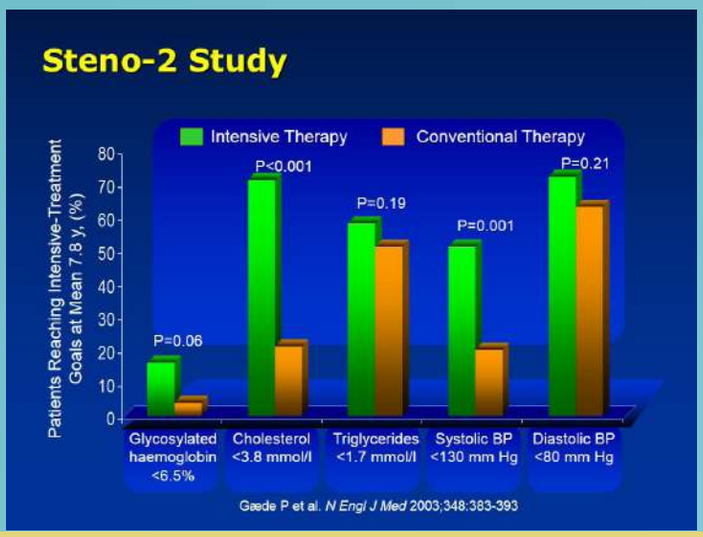
Postprandial glycemic excursions become more predominant in patients with good control of fasting plasma glucose. Therefore, treatment should focus on both FPG and PPG excursions in order to reach and maintain A1C targets.

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.

SLIDE 17



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%.



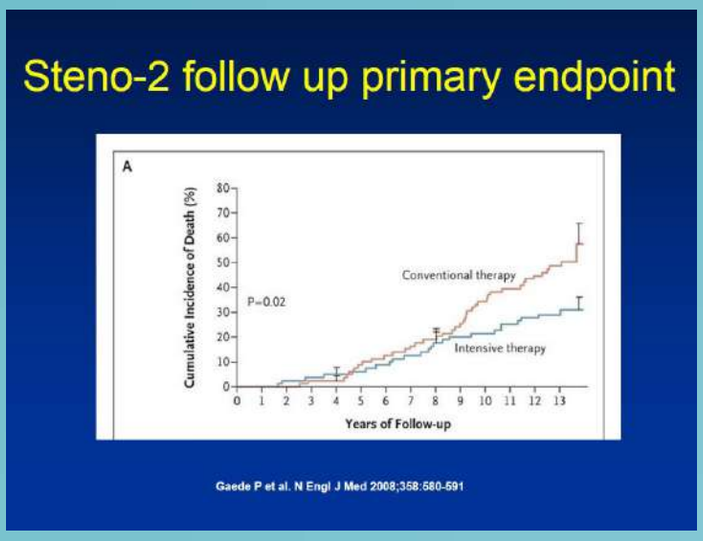
Efficacy of multiple risk factor intervention in high-risk subjects (type 2 diabetes with microalbuminuria): Steno-2

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:

Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-393.

SLIDE 19



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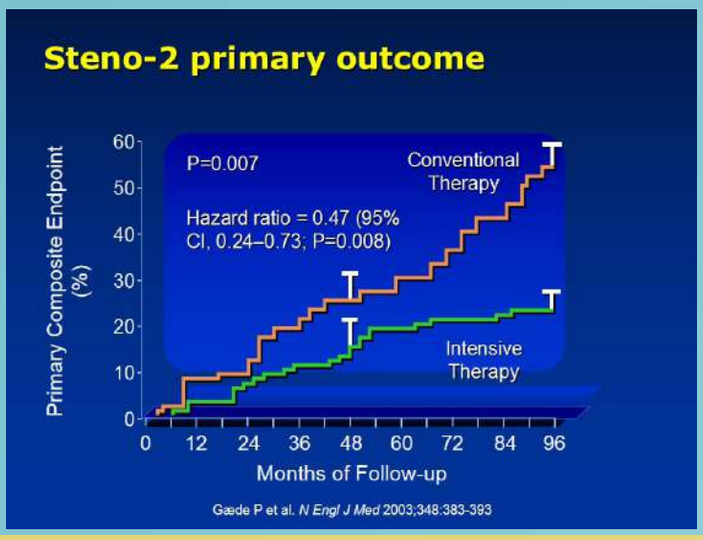


Composite endpoint of death from CV causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation, or surgery for PAD: Steno-2

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:

Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-393.

SLIDE 21

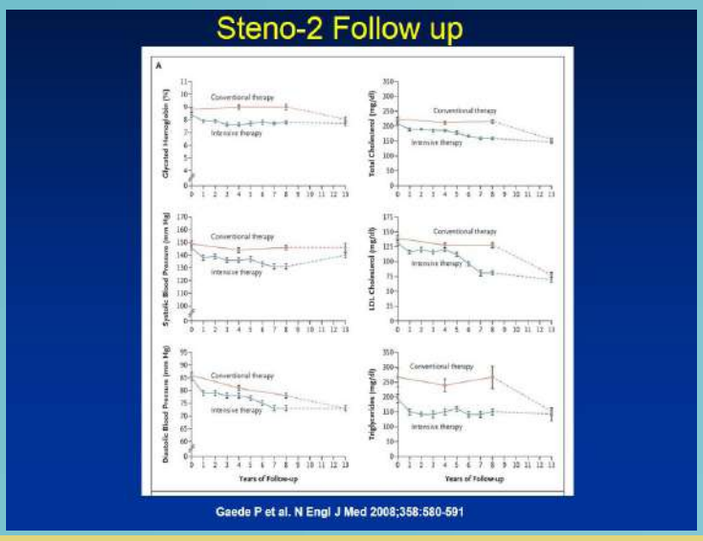
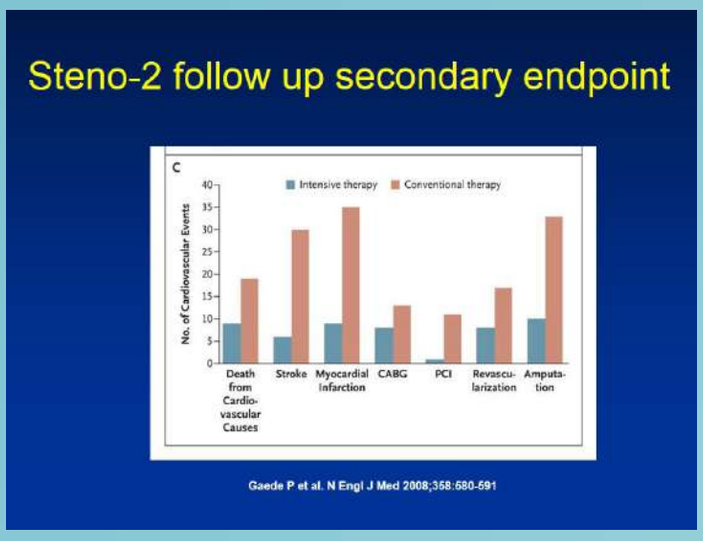


Figure 2. Changes in Selected Risk Factors during the Interventional Study and Follow-up Period. Panel A shows mean ({+/-}SE) values for selected risk factors during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines). In the conventional-therapy 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 22



SLIDE 23

Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of Complication
Blood glucose control	Heart attack	↓ 37%[1]
Blood pressure control	Cardiovascular disease	↓ 51%[2]
	Heart failure	↓ 56%[3]
	Stroke	↓ 44%[3]
	Diabetes-related deaths	↓ 32%[3]
Lipid control	Coronary heart disease mortality	↓35%[4]
	Major coronary heart disease event	↓55%[5]
	Any atherosclerotic event	↓37%[5]
	Cerebrovascular disease event	↓53%[4]

[1] UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.
[2] Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[3] UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[4] Grover SA, et al. *Circulation*. 2000;102:722-727.
[5] Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.

SLIDE 24

Glucose lowering – waste of time?

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

SLIDE 25

When and how should glucose monitoring be used?

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 FPG or PPG for any individual patient

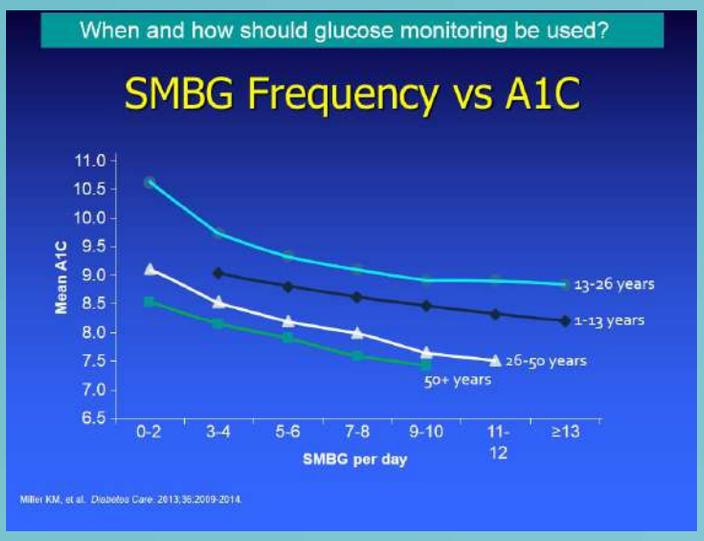
Testing positively affects glycemia in T2D when the results are used to:
- Modify behavior
- Modify pharmacologic treatment

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

SMBG, self-monitoring of blood glucose.

SLIDE 26



SLIDE 27

Targets for Control

Parameters		Levels
Glycaemic control*	Pasting or pre-prandial	4.4 – 7.0 mmol/L
	Post-prandial**	4.4 – 8.5 mmol/L
	A1c++	≤6.5%
Lipids	Triglycerides	≤1.7 mmol/L
	HDL-cholesterol	>1.0 mmol/L (male)
		>1.2 mmol/L (female)
	LDL-cholesterol	≤2.6 mmol/L#
Blood pressure		≤135/75 mmHg$
Exercise		150 minutes/week
Body weight	If overweight or obese, aim for 5-10%weight loss in 6 months	

- Modified from the NICE guideline: Type 2 diabetes: The management of type 2 diabetes, 2009. 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 col laborated 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.

TOPIC

3

Case Study

targets for control

SLIDE 1

Case 1

A 45-year-old male, teacher.

Diagnosed T2DM for 3 years, referred for further management of diabetes.

Current BMI:31.2 kg/m^2
BP:125/74 mmHg, waist: 102 cm

Medications:

- Metformin 850 mg BD
- Diamicron MR 60 mg daily
- Lipitor 10 mg OD
- Aprovel 150 mg OD

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

SLIDE 2

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.

SLIDE 3

What is the target of A1c in this patient?

- Target A1c is between 6.0 – 6.5% because he is young and newly diagnosed DM.

How are you going to achieve this?

1. Should stress about lifestyle modification e.g. diet, exercise and healthy eating, doing this should be able to bring down A1c level
2. Failing all the above then the third agent will be discussed.

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/m^2

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 umo/L
- E-GFR : 56 ml/min/1.73 m2
- TG : 2.11 mmol/L
- T-Chol : 5.12 mml/L
- LDL-C : 2.74 mmol/L
- HDL-C : 1.1 mmol/L

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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.

SLIDE 7

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/m^2
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 mmolL
- 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.

TOPIC

4

Lecture Notes

medical nutrition therapy & low glycaemic index diet

SLIDE 1

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

SLIDE 2

General recommendations

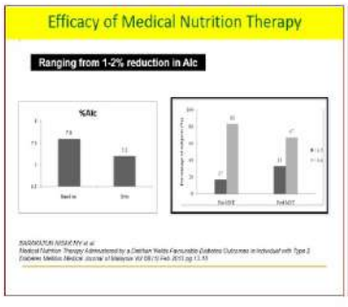
Nutrition care by a dietitian should be provided under the following conditions:

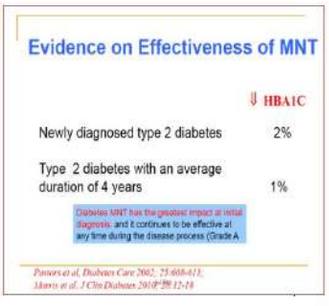
- at diagnosis
- sub-optimal metabolic and/or weight control
- at initiation of insulin therapy
- development of other co-morbidities such as hyperlipidaemia, hypertension and chronic kidney disease.

SLIDE 3

General recommendations

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





SLIDE 4

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 ½-1 kg per week. [50 (Level I)]

Physical activity of 150 minutes per week i.e. 30 minutes five days or more per week. [51 (Level I)]

Meal replacements (MRPs) can be used as part of a comprehensive meal plan for weight loss and weight maintenance. [52 (Level I)]

A combination of reduced calorie diet, physical activity and behaviour modification can provide greater initial weight loss. [51 (Level I)]

SLIDE 5

Quick Guide of Selecting The Right MRP

Calories	**190 to 250**	For MRPs fewer than 200 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.
Protein	10 to 15 grams	Adequate protein promotes health and mealtime fullness.
Carbohydrate	14 to 34 grams	To slow the rate blood glucose (sugar) rises after a meal, look for the first carbohydrate listed in the ingredients to be maltodextrin or tapioca dextrin rather than refined sugars, such as sucrose, corn syrup, high-fructose corn syrup or brown rice syrup.
Dietary Fiber	**3 to 6 grams**	
Total Fat	5 to 8 grams	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.
Cholesterol	0 to 20 milligrams	
Sodium	100 to 300 milligrams	
Vitamins and Minerals	Look for 50 to 100 percent of the Dietary Reference Intake.	
Avoid products containing stimulants, such as caffeine, ginseng, guarana and ephedra.		

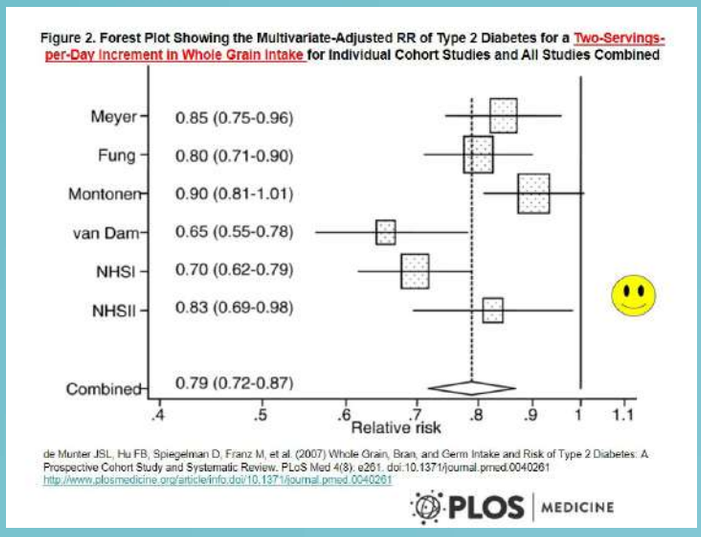
SLIDE 6

Specific recommendations: Prevention of Diabetes

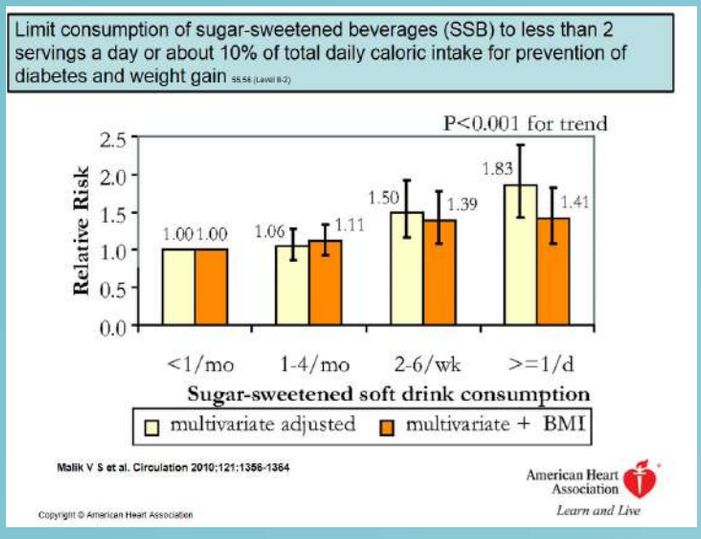
A high dietary fiber diet is encouraged for the prevention of diabetes . A high fibre diet (20–30 g fibre/day) consisting of vegetables, fruits, legumes and whole grain cereals is encouraged. [54 (LevelII-2)] Higher consumption of whole grains can contribute to the prevention of T2DM. [54 (Level II-2)]

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

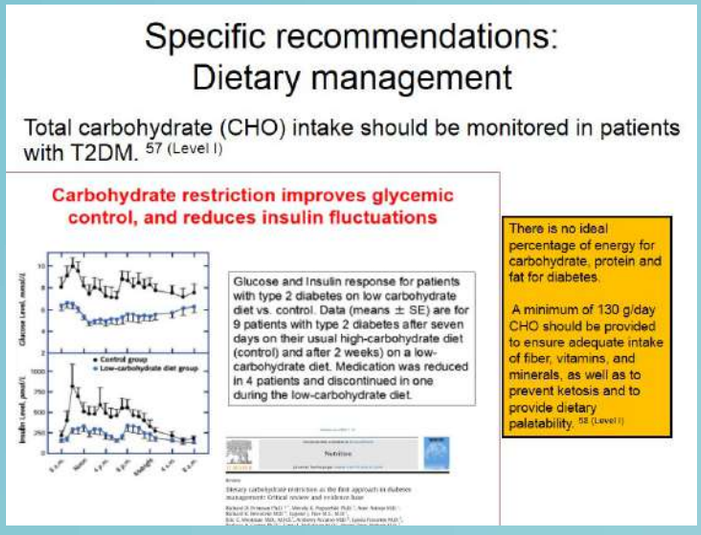
SLIDE 7



SLIDE 8



SLIDE 9



SLIDE 10

SLIDE 11

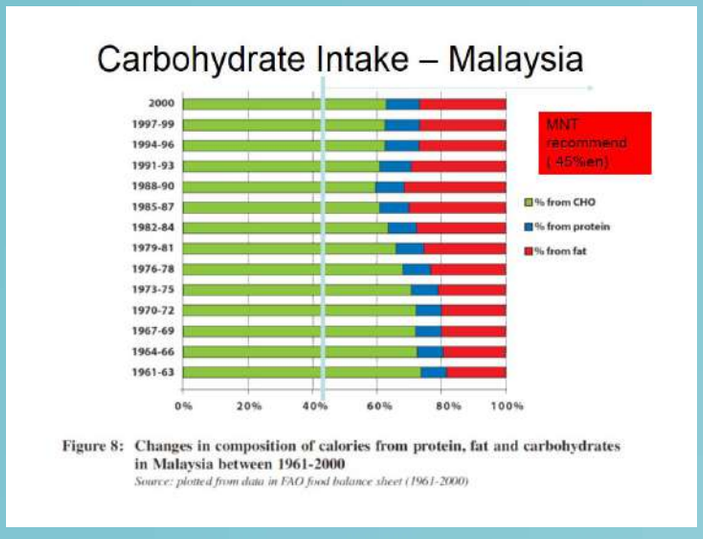
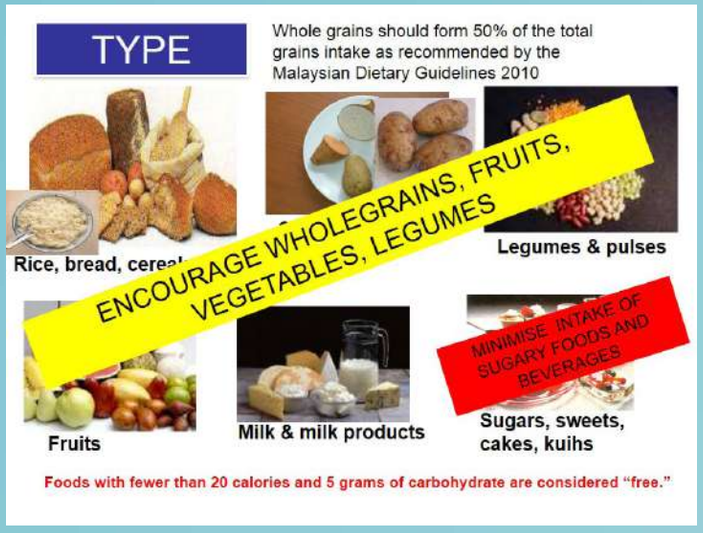


Figure 8: Changes in composition of calories from protein, fat and carbohydrates in Malaysia between 1961-2000
Source: plotted from data in FAO food balance sheet (1961-2000)

SLIDE 12



SLIDE 13

AMOUNT

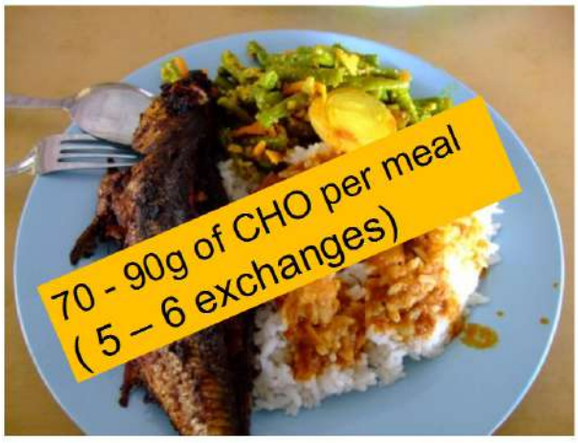
Total CHO percentage of 45 to 60% of total energy is recommended. The percent depends on weight, glycemic & other metabolic goals, cultural preferences and individual lifestyle

1 cup noodles/Rice/Starchy vegetable ~ one cupped hand *(2 exchanges)*

½ cup rice/noodles
1 serve of fruit *(1 exchange)*

Population	Carb choices (meal)
Inactive women	2-4
Active women or inactive men	3-5
Active men	4-6
	Carb choices (snack)
Between meal or HS Snacks	1-2

SLIDE 14



SLIDE 15

How much cereals per meal ?

Breakfast / Lunch/ Dinner

Noodle 1- 1 ½ cup | Whole meal bread 2-3 slices | Rice 1- 1 ½ cup

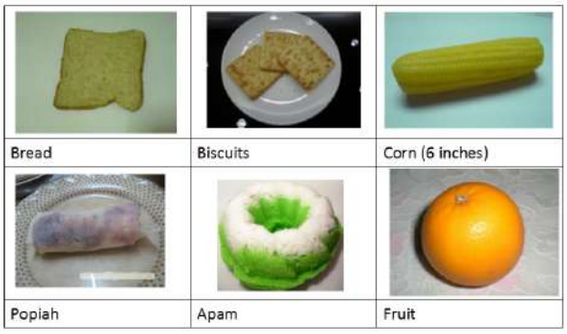
Oat 6 tbsp | Biscuits 6 pcs | Capati 1 pc

* Suitable for sedentary women & inactive men

Based on 2-4 exchanges of CHO per meal. This is for 1600-1800 kcal a day.

SLIDE 16

What about snacks?



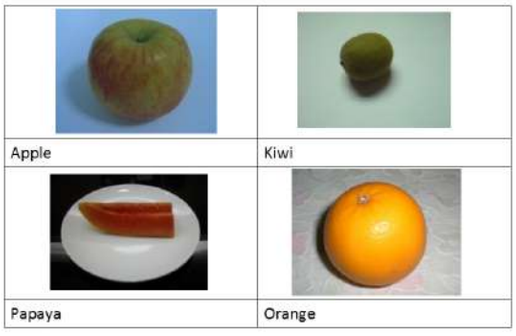
Bread	Biscuits	Corn (6 inches)
Popiah	Apam	Fruit

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?



Apple	Kiwi
Papaya	Orange

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

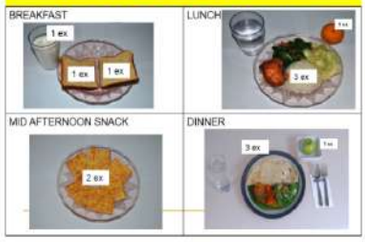
CHO intake must be kept consistent on a day-to-day basis if patient is on diet therapy alone, oral anti-diabetic agents (OADs) or fixed insulin regime.

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.

Carbohydrate distribution



SLIDE 19

1 CHO exchange = 15g CHO, 65kcal

Honey	1 teaspoon
Jam	1 teaspoon, 1 teaspoon
Kaya	1 teaspoon, 1 teaspoon, 1 teaspoon
Sugar	1 teaspoon, 1 teaspoon, 1 teaspoon
Syrup	1 teaspoon, 1 teaspoon, 1 teaspoon
Cocoa/ Malt-based Powder	1 teaspoon, 1 teaspoon
Condensed Milk	1 tablespoon, 1 tablespoon
Candy	1 teaspoon, 1 teaspoon, 1 teaspoon

1 teaspoon= 5g

1 tablespoon = 10 g

Sucrose (e.g. table sugar) intake must be counted as part of the total carbohydrate intake.[59(Level III)]

Excess sucrose intake contributes to calories and may cause weight gain.

60 (Level I)

SLIDE 20

efsa

European Food Safety Authority

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)

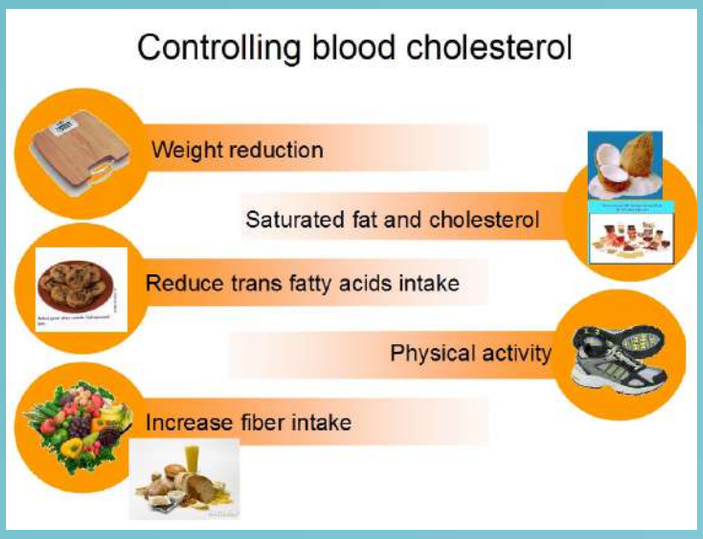
Non-nutritive sweeteners do not impact glycaemic level. [56,60 (Level II-2)]
Intake should not exceed Acceptable Daily Intake (ADI) levels.

SLIDE 21

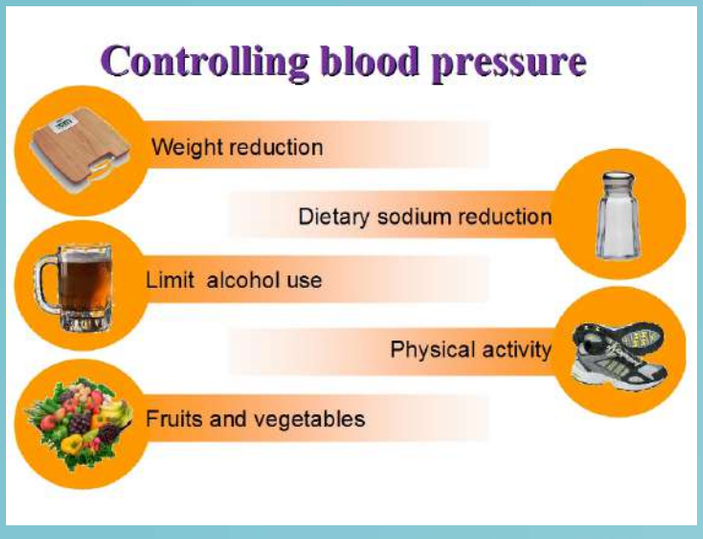
Patients with diabetes have the same vitamin & mineral requirements as the general population. There is no clear evidence of benefit from the use of antioxidant vitamins A, C, E, selenium and herbs and omega-3 fatty acids in diabetes management. [65 (Level I)]

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. [49 (Level II)]

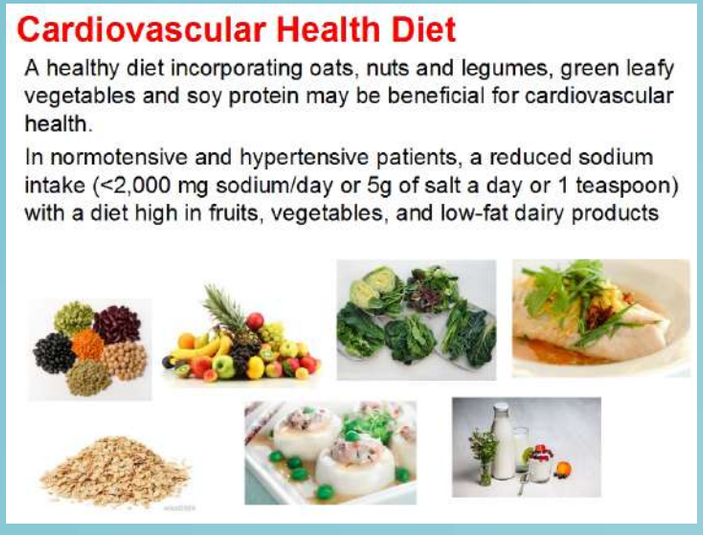
SLIDE 22



SLIDE 23



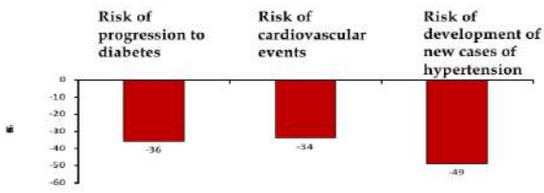
SLIDE 24



SLIDE 25

Post-prandial hyperglycemia

Effects of Reducing PPHG



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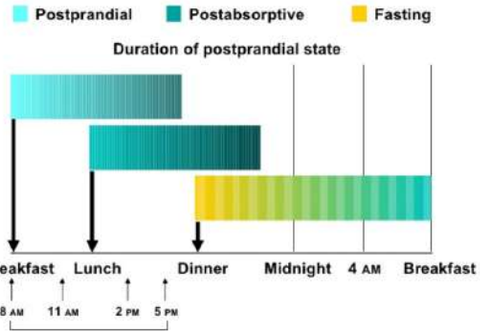
SLIDE 26

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



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Adapted from Monnier L. *Eur J Clin Invest.* 2000;30(suppl 2):3-11.

SLIDE 27

Non-pharmacological treatment for PPG

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

SLIDE 28

Definition of Glycemic Index

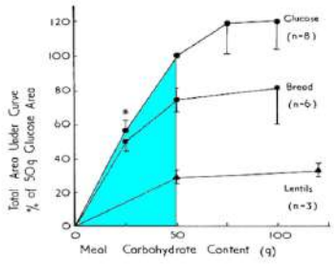


Fig 1: The original glycaemic index graph from Jenkins and colleagues 1981

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 .

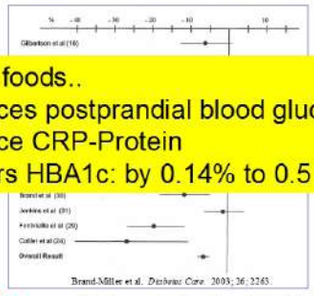
Ref: *F Xavier Pi-Sunyer* , AJCN 2002

SLIDE 29

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 %

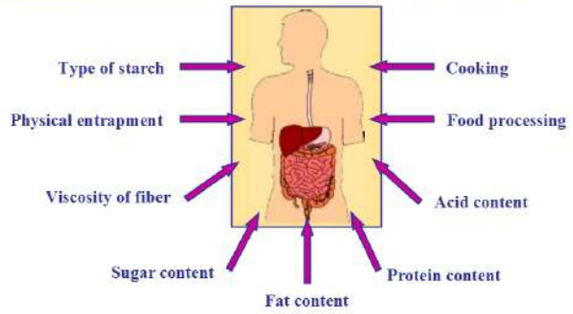
Brand-Miller et al. *Diabetes Care* 2003; 26: 2261.

Mean difference

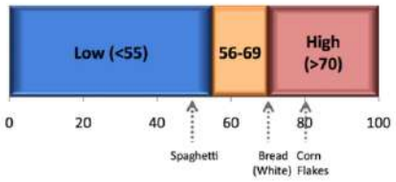
- **0.43% points in HbA1c** ***over & above*** reduction from high GI diet

SLIDE 30

Factors Influencing GI Ranking



SLIDE 31



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

APPENDIX 3 Glycaemic Index of Foods [454-458 (Level III)]

Food Category	Low GI (<55)	Intermediate GI (55-70)	High GI (>70)
Rice	Barley	Basmati Rice Brown rice Parboiled rice Red rice	Glutinous rice Jasmine rice Instant porridge White rice Sago
Bread and cereals products	All bran breakfast cereals Muesli Wholegrain bread varieties	Capati Idli Oatmeal Pita bread, wholemeal Wholemeal barley flour bread	Cornflakes Rice crackers Roti Canai White flour bread Wholemeal (whole wheat) wheat flour bread
Noodle and Pasta	Lasagne pasta sheets, Spaghetti, white, boiled Spaghetti, wholemeal, boiled	Spaghetti, white, durum wheat semolina Udon noodles, plain Wheat noodles	Fried macaroni Fried meehoon Fried rice noodles Rice noodle (*kuih teow*)

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]

TOPIC

4

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.

SLIDE 4

Physical Examination

Weight: 80 kg; Height: 1.65 m; BMI: 29.4 kg/m^2
Waist circumference: 110 cm
Blood pressure: 140/90 mmHg (sitting), Pulse 70 beats/min
Respiratory rate: 20 breaths/min
Temperature: normal

SLIDE 5

Blood results

	Results
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

SLIDE 6

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
- Dosei 6" 2 pieces @ white/wholemeal bread 2-3 pieces @ idli/capati 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 kuihs 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
- ❑ Hyperlipidemia
- ❑ Hypertension
- ❑ Self management /lifestyle deficits
- ❑ Postprandial hyperglycemia
- ❑ Cardiovascular risk
- ❑ Retinopathy
- ❑ Nephropathy
- ❑ Peripheral Neuropathy
- ❑ Sedentary lifestyle
- ❑ Poor dietary habits
- ❑ Elevated urine microalbumin level
- ❑ Metabolic Syndrome

SLIDE 10

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**

SLIDE 11

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**

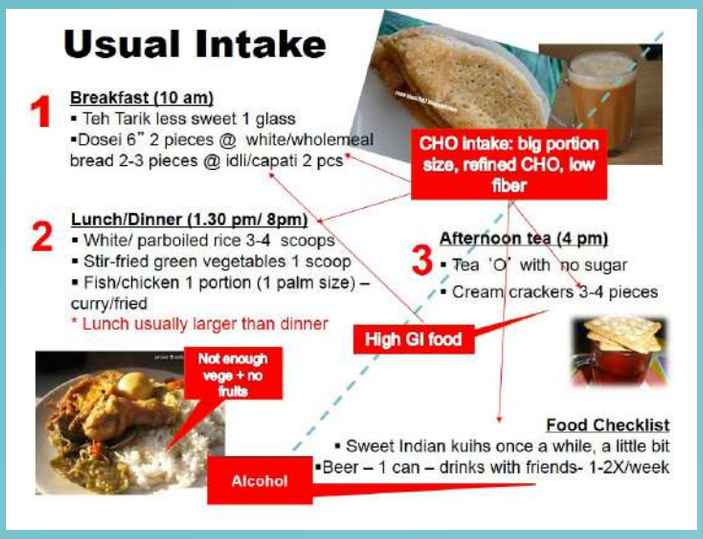
SLIDE 12

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

SLIDE 13



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**

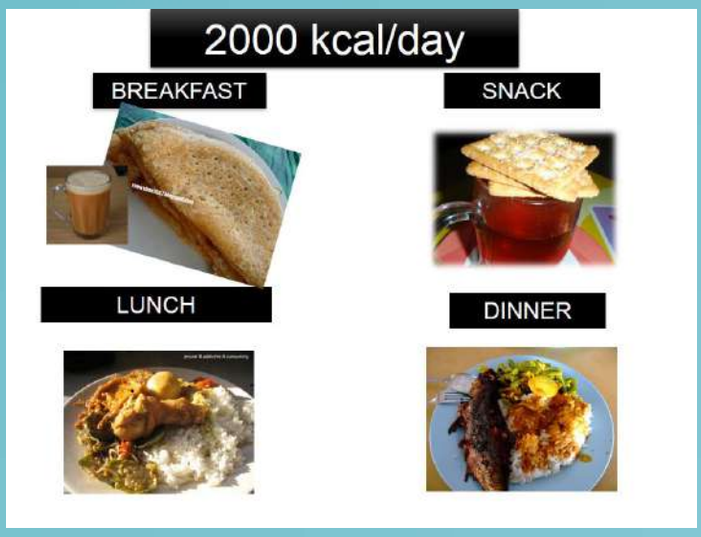
SLIDE 15

Question 6

What changes should Mr LG do to his diet?

- ❑ **Use meal replacements**
- ❑ Skip dinner and substitute with oats
- ❑ Avoid rice, dosei, 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**

SLIDE 16



SLIDE 17

SLIDE 18

SLIDE 19

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**

SLIDE 20

Question 8

What other lifestyle changes can he make?

- Increase physical activity or exercise

SLIDE 21

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).

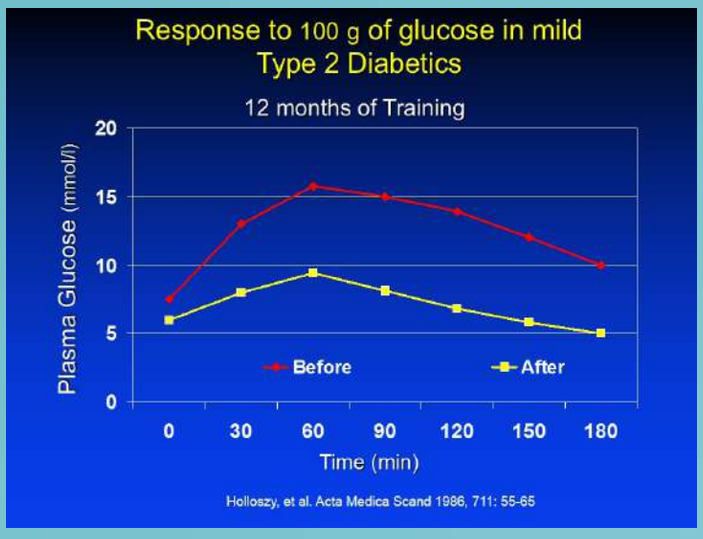
TOPIC

5

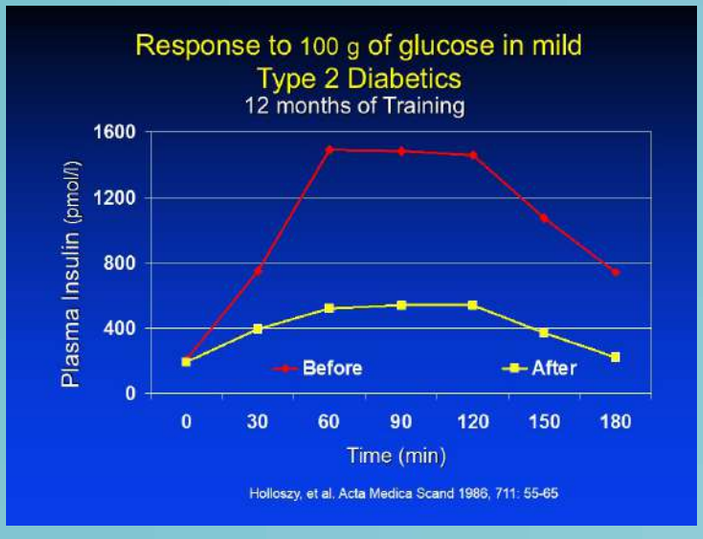
Lecture Notes

physical activity

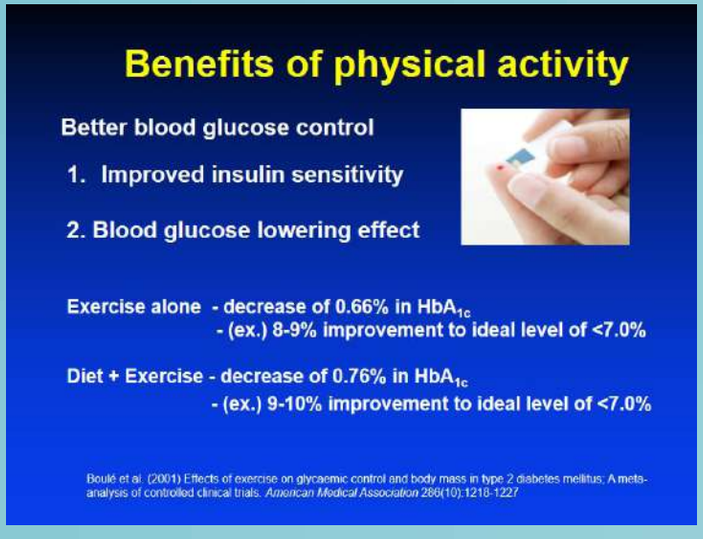
SLIDE 1



SLIDE 1



SLIDE 3



SLIDE 4

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).

SLIDE 5

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

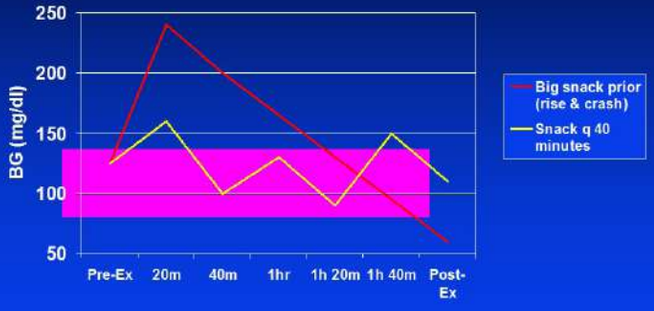
BG low or dropping: ⇧ usual carbs
BG OK or stable: usual carbs
BG High or rising: ⇩ usual carbs

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

SLIDE 6

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



Source: Scheiner, Gary, MS CDE

SLIDE 7

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.

SLIDE 8

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.

SLIDE 9

Recommendations 3 and 4

3. The duration of exercise should be at least 150 minutes/week of moderateintensity 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

TOPIC

5

Case Study

physical activity

SLIDE 1

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.

SLIDE 2

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

SLIDE 3

Case

Clinical examination:

Height: 1.62 m, Weight: 88.1 kg, BMI: 33.6 kg/m^2
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.

SLIDE 4

Comment on her BMI?

- BMI range: obese class 1.
- Sedentary lifestyle

What are her risk factors?

- Age over 30 years
- BMI = 33.6 kg/m^2 - obese
- WC >80 cm (for women) – central obesity
- Sedentary lifestyle
- Combination of several NCD risk factors - She is at high risk.

SLIDE 5

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

SLIDE 6

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.

SLIDE 7

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.

SLIDE 8

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.

SLIDE 9

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.

SLIDE 10

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.

SLIDE 11

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.

SLIDE 12

Small changes make a "weight" difference

	Daily	Yearly	
	Reduced Intake/ Expenditure (kcal)	Total Intake/ Expenditure (kcal)	**Weight equivalent (kg)**
Slow walk for 30 mins/day	89	32,485	**-4.2 kg**
Brisk walk for 30 mins/day	130	47,085	**-6.1 kg**
Jog for 30 min/day	252	91,980	**-11.9 kg**
Reduce intake of 2 tsps sugar/day	40	14,600	**-1.9 kg**
Reduce intake of 2 tsps oil/day	90	32,850	**-4.3 kg**
Switch to drink lemon tea (no sugar) instead of milk tea	113	41,245	**-5.4 kg**
Drink 1 can less of soft drink/day	150	54,750	**-7.1 kg**

Courtesy from Dr Ronald Ma CW, H. Kong

TOPIC

6

Lecture Notes

oral anti-diabetic medications

SLIDE 1

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

2

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

3

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.

4

SLIDE 4

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

5

SLIDE 5

Metformin Formulations and Dosage

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

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

6

SLIDE 6

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

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SLIDE 7

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

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SLIDE 8

SU Formulations and Dosage

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

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

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

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SLIDE 9

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

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SLIDE 10

Meglitinides (cont.)

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

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

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SLIDE 11

Alpha-glucosidase 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

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SLIDE 12

Alpha-glucosidase 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

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

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SLIDE 13

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

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SLIDE 14

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.

Formulation	Minimum dose	Maximum dose
Rosiglitazone 4 / 8 mg tablet	4 mg OD	8 mg OD
Pioglitazone 15 / 30 mg tablet	15 mg OD	45 mg OD

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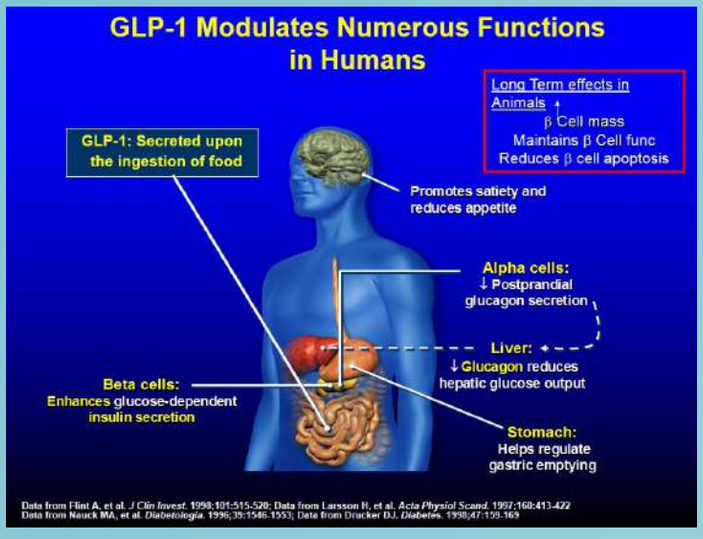
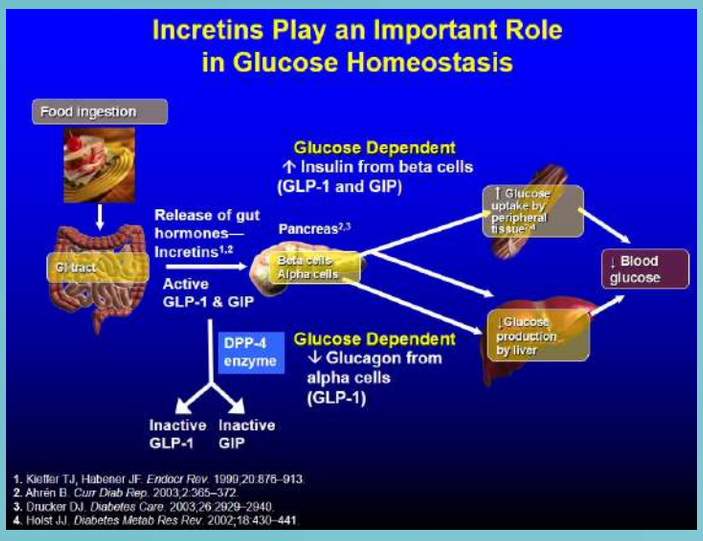
SLIDE 15



SLIDE 16



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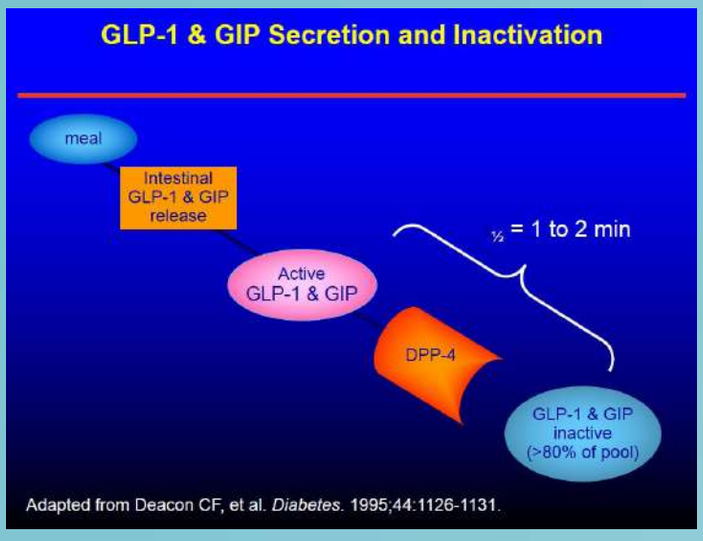

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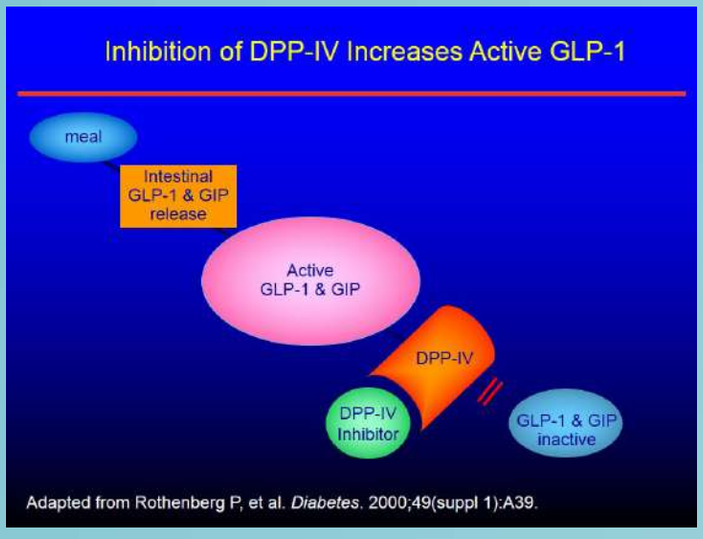

SLIDE 19

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

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SLIDE 20

DPP-4 Inhibitors Formulations and Dosage

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

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

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SLIDE 21

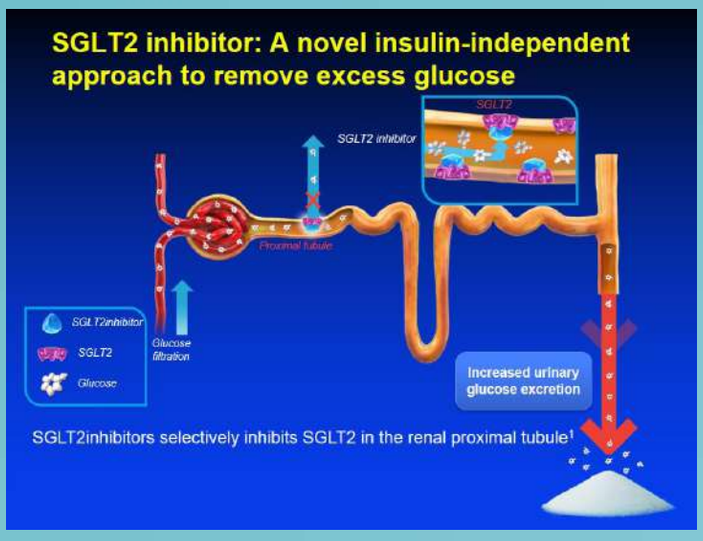
DPP-4 Inhibitors: A Pharmacokinetic Comparison

Agent	Dosing	mg	$t_{1/2}$ (hr)	Metabolism	Excretion
Sitagliptin[a]	qd	100	~12	Unchanged	> 80% urine
Vildagliptin[b]	bid	50	~3	Inactive metabolites	~85% urine
Saxagliptin[c]	qd	5	~3	Active metabolite	> 60% urine
Linagliptin[d]	bid	5	> 10	Mostly unchanged	~80% bile

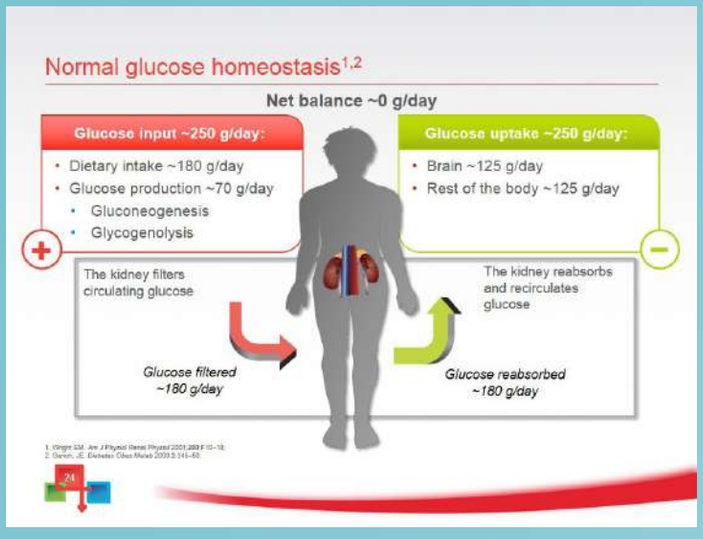
bid = twice daily; qd = once daily; $t_{1/2}$ = half-life

a. Vincent SH, et al. *Drug Metab Dispos.* 2007;35(4):533-538.
b. He H, et al. *Drug Metab Dispos.* 2009;37(3):545-554.
c. Bristol-Myers Squibb Company, AstraZeneca Pharmaceuticals LP. http://packageinserts.bms.com/pi/pi_onglyza.pdf
d. Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Tradjenta/Tradjenta.pdf

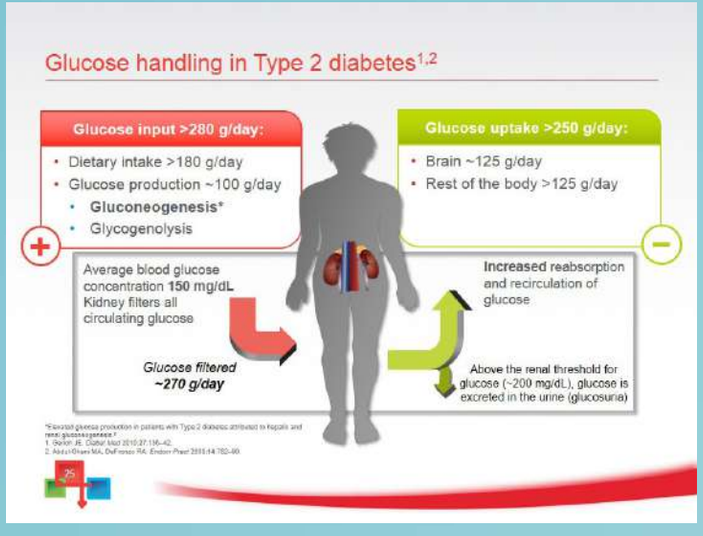
SLIDE 22



SLIDE 23



SLIDE 24



SLIDE 25

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 m^2)

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SLIDE 26

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.

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SLIDE 27

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.

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SLIDE 28

SGLT2 Inhibitors Formulations and Dosage

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

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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.

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SLIDE 30

What Comes After Metformin? Depends …

Patient characteristics	Drug characteristics
Degree of hyperglycemia	BG lowering efficacy & durability
Risk of hypoglycemia	Risk of inducing hypoglycemia
Weight	Effect on weight
Comorbidities (renal, cardiac, hepatic)	Contraindications & side effects
Access to treatment	Cost and coverage
Patient preferences	Other

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.

SLIDE 31

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.

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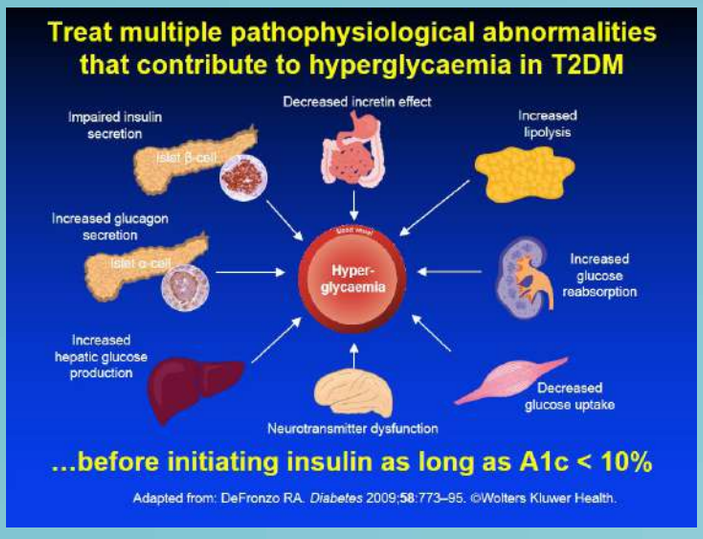
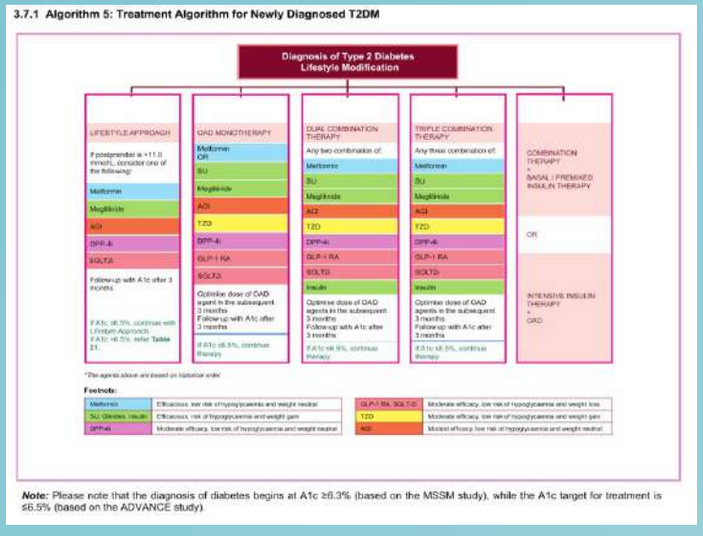
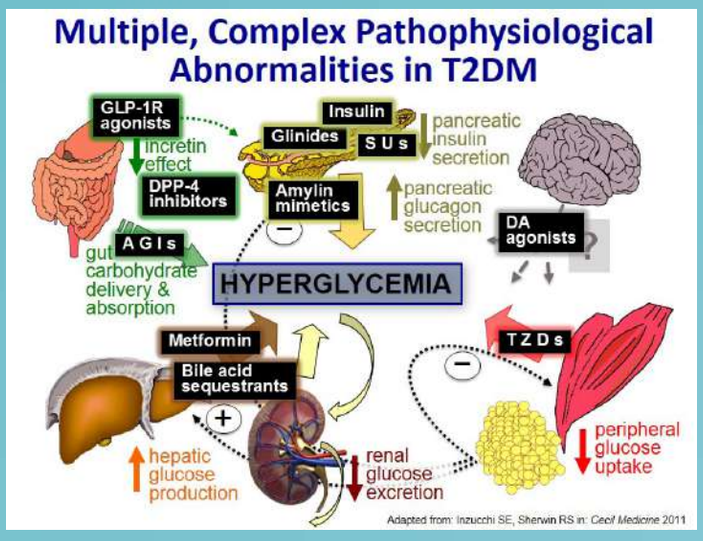
SLIDE 32



SLIDE 33



SLIDE 34



SLIDE 35

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

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

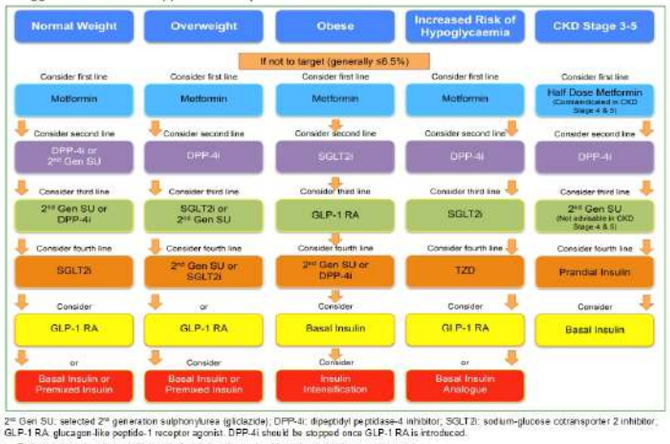
MDI = Multiple daily injections; [§] Intensify involves changing the regimen; SU = sulphonylureas

Box 1: Selection of Anti-diabetic Agents

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

SLIDE 36

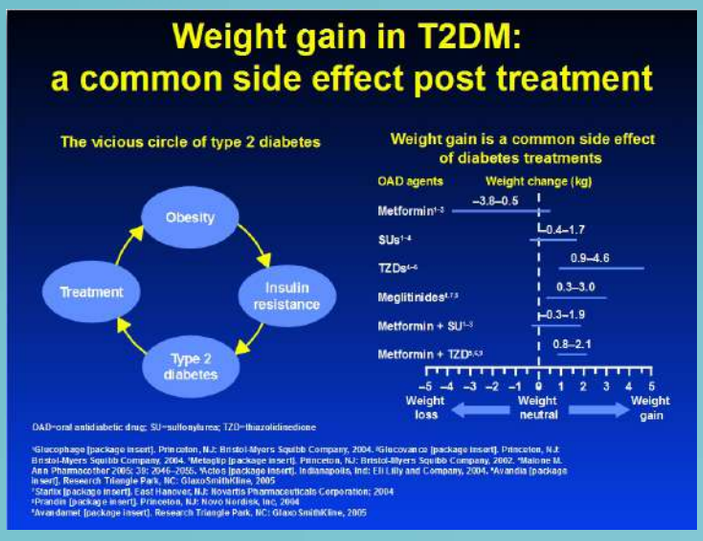
Suggested Treatment Approach for Specific Patient Profiles



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

- Patients who are well-controlled on their existing drugs should continue with the treatment regime.
- Bariatric surgery may be considered in patients with BMI ≥32 kg/m² and their diabetes not controlled by lifestyle changes and pharmacotherapy [37]

SLIDE 37



SLIDE 38

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

✓ Acceptable to use X Do not use

Agent	Metabolites	Route of Elimination	eGFR (mL/min) > 60	60-30	< 30	< 15
Metformin[a,b]	Unchanged	~ 100% urine	✓	✓*	X	X

- Metformin is eliminated renally, and (rare) cases of lactic acidosis have been described in CKD patients[a]
- In T2DM patients[b]:
  - Reduce dose if GFR < 45 mL/min
  - Do not use if GFR < 30 mL/min

*Dose adjustment required

a. Lalau JD. *Drug Saf.* 2010;33(9):727-740.
b. NICE Clinical Guidelines. http://www.nice.org.uk/CG87
Slide courtesy of Clifford J. Bailey, PhD.

SLIDE 39

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

✓ Acceptable to use ? Use with caution X Do not use

Agent	Metabolites	Route of Elimination	eGFR (mL/min) > 60	60-30	< 30	< 15
Glimepiride	Active	~ 60% urine	✓	✓*	X	X
Glipizide	Inactive	~ 70% urine	✓	✓	X	X
Gliclazide	Inactive	~ 65% urine	✓	✓	?	X

*Dose adjustment required

Lubowsky ND, et al. *Am J Kidney Dis.* 2007;50(5):865-877.
Hamilton CA. *J Ren Care.* 2012;38(Suppl 1):59-66.
Slide courtesy of Clifford J. Bailey, PhD.

SLIDE 40

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

✓ Acceptable to use X Do not use

Agent	Metabolites	Route of Elimination	eGFR (mL/min) > 60	60-30	< 30	< 15
Repaglinide	Inactive	~ 90% bile	✓	✓	✓*	X
Pioglitazone	Active	~ 55% bile	✓	✓	✓	X
Acarbose	Metabolites formed in gut	~ 2% urine	✓	✓	X	X

*Dose adjustment required

Bolignano D, et al. *Nutr Metab Cardiovasc Dis*. 2012;22(3):167-175.
Hamilton CA. *J Ren Care*. 2012;38(Suppl 1):59-66.
Slide courtesy of Clifford J. Bailey, PhD.

SLIDE 41

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

✓ Acceptable to use ? Use with caution X Do not use

Agent	Metabolites	Route of Elimination	eGFR (mL/min) > 60	60-30	< 30	< 15
Exenatide	Mostly eliminated through glomerular filtration	Mostly urine	✓	?	X	X
Liraglutide	Degraded in the circulation, liver, and kidney	Partly urine	✓	?	X	X
Insulin	Degraded in the circulation, liver, and kidney	Partly urine	✓	✓*	✓*	✓*

*Dose adjustment required

Fonseca VA. *Am J Med*. 2011;124L554-561.
Hamilton CA. *J Ren Care*. 2012;38(Suppl 1):59-66.
Slide courtesy of Clifford J. Bailey, PhD.

SLIDE 42

Efficacy of Various Anti-diabetic Agents

	MET	SU	GLN	AGI	TZD	DPP4-i	SGLT2-i	GLP-1 RA	Insulin
A1c reduction, %	1.0-1.5	0.4-1.6	1.0-1.2	0.5-0.8	0.5-1.4	0.5-0.8	0.2-0.8	0.5-1.4	>1.5
FPG vs PPG	FPG	FPG	Both	PPG	FPG	Both	Both	Both	Both
Hypoglycaemia	↔	↑↑	↑	↔	↔	↔	↔	↔	↑↑
Weight change	↓	↑↑	↑	↔	↑↑	↔	↓↓	↓↓	↑↑
GI symptoms	↑↑	↔	↔	↑↑	↔	↑	↔	↑↑	↔
Congestive heart failure	↔	↔	↔	↔	↑	↔	↔	↔	↔
Cardiovascular disease	↓	↔?	↔	↔	↔	↔	↓?	↔	↔
Bone loss	↔	↔	↔	↔	↑	↔	↔	↔	↔
CKD	Avoid if GFR<30	Hypo-glycaemia	Hypo-glycaemia	↔	Fluid retention	Dose adjustment	Avoid if GFR<60	Avoid if GFR<30	Hypo-glycaemia
References	77 (Level I)	168,169 (Level I)	85 (Level I)	170 (Level I)	86-92 (Level I)	151-153 (Level I)	113-118 (Level I)	121 (Level I)	160,161,171, 172 (Level I)

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

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

Beneficial Possible benefit Neutral Minimal risk Increased risk

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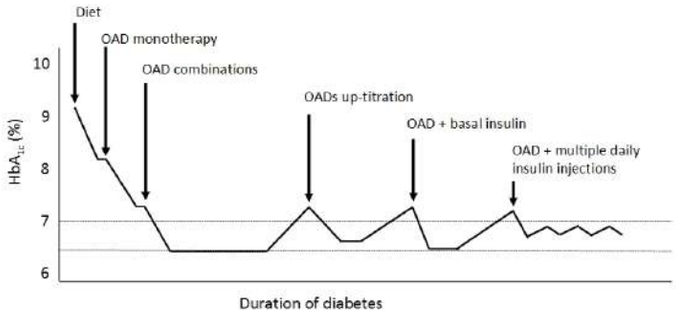
SLIDE 43

Proactive management of glycaemia: Early combination approach



44

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

45

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."

Nathan DM.
Finding new treatments for diabetes--how many, how fast...how good?
N Engl J Med. 2007;356(5):437-40.

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.

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TOPIC

6

Case Study

oral anti-diabetic medications

SLIDE 1

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/m^2
Acanthosis nigricans noted
BP 140/79 mmHg

Current treatment:

- Metformin 1 gm TDS
- Perindopril 4 mg od
- Indapamide 1.5 mg od

SLIDE 2

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

SLIDE 3

How would you manage this patient?

- Add GLP1-RA or SGLT2i
- Look for obesity related complications:
  - OSA, OA, heart failure

SLIDE 4

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

SLIDE 5

Case 2

Mr. D.K., a 50-year-old Indian man
Weight 64.5 kg; BMI 22.5 kg/m^2
Has family history of diabetes
Duration of diabetes: 5 years
A1c 8.6%
Current medications:
Metformin 250 mg TDS
Gliclazide 80 mg BD

SLIDE 6

What are your comments on the management of this patient initially?

- Poor glycaemic control, not reaching target
- Increase dose of OADs

SLIDE 7

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

SLIDE 8

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

SLIDE 9

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 ccasional '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 gliclazide 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/m^2

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

TOPIC

7

Lecture Notes

insulin therapy & injectables

SLIDE 1

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).

SLIDE 2

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*

SLIDE 3

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:

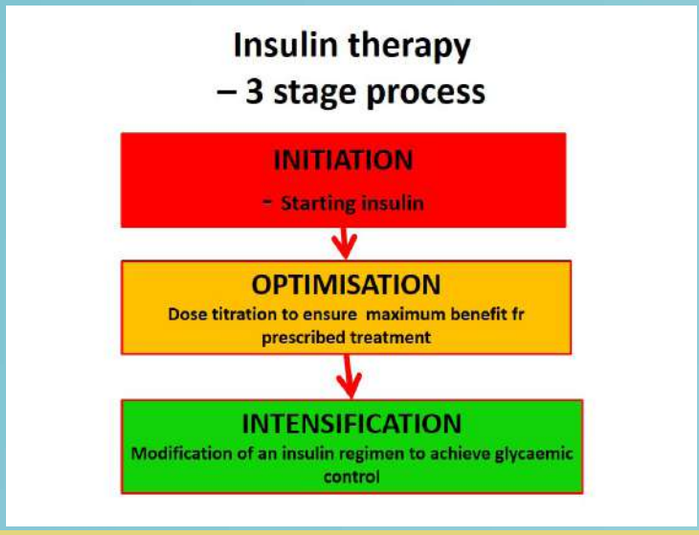
- **Prandial insulin** is administered pre-meal because of its short or rapid onset of action in controlling post-prandial glucose excursion.
- **Basal insulin** is administered once or twice daily and covers the basal insulin requirements in between meals and overnight.
- **Premixed insulin** is biphasic 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.

SLIDE 4

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

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.

SLIDE 5



Implementing successful insulin therapy requires a 3 - stage process;
Initiation – Starting insulin. Requires selection of appropriate insulin regimen, insulin type and starting dose to address the individual's main glycemic abnormality.
Optimisation – Dose titration / adjustment. Requires gradual, safe and prompt titration of insulin dose according to self blood glucose monitoring (SMBG) towards an optimal dose to ensure maximum benefit from prescribed treatment. The insulin dose should be adjusted at least weekly to get the monitored readings to target. Optimisation of the insulin dose should be an interactive process between the healthcare provider and the patient. \

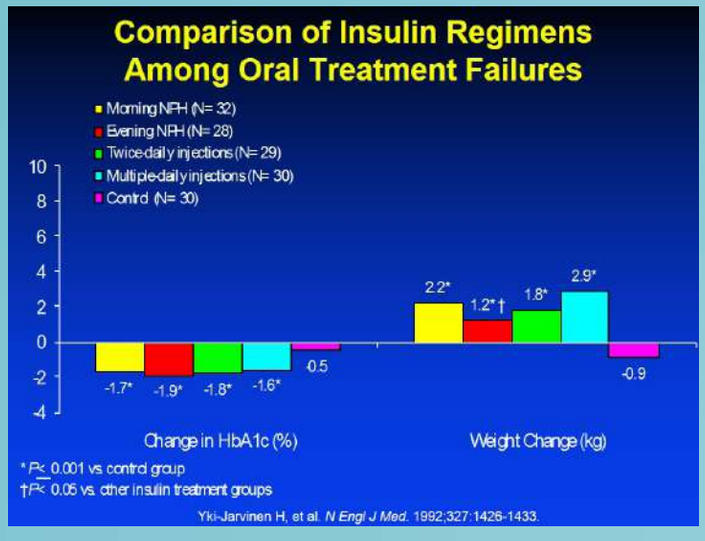
This can be done at the diabetic resource centre or via telephone calls. It should be done within the first few months of starting insulin.
Intensification - Modification of an insulin regimen to achieve better glycaemic control. Requires switching to more intensive insulin regimens for better glycaemic control.

SLIDE 6

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.

SLIDE 7



SLIDE 8

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

SLIDE 9

Optimising Insulin doses

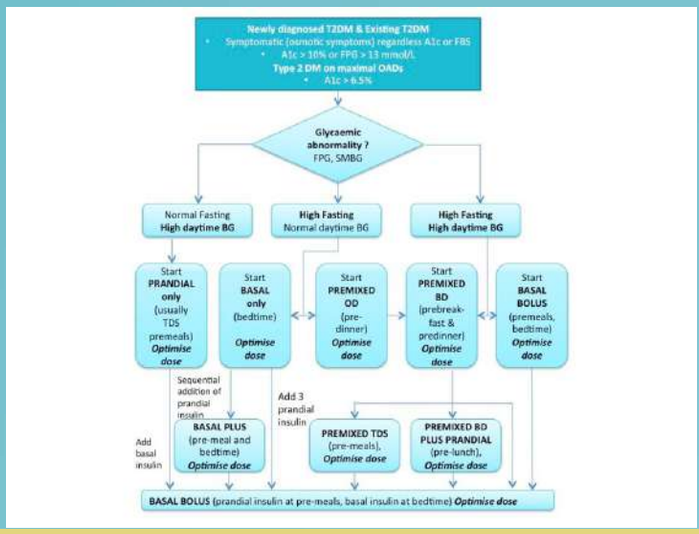
- Insulin dose optimisation requires gradual, safe and prompt titration of insulin dose according to SMBG.
- The insulin dose should be adjusted at least weekly within the first 3 months of starting insulin to achieve glycaemic targets.
- Optimisation of the insulin dose should be an interactive process 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.

SLIDE 11



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.

SLIDE 12

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

SLIDE 13

Monitoring Insulin Therapy

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

SLIDE 14

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.

SLIDE 15

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.

SLIDE 16

SMBG in Basal/Basal Bolus Regimen

	Fasting Glucose	Post-Break fast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Pre-bed
Basal Insulin Only	X						
Basal Bolus (short-acting insulin)	X		X		X		X
Basal Bolus (rapid-acting insulin)	X	X		X		X	

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 (analogues).

SLIDE 17

SMBG in Premixed Insulin

	Fasting Glucose	Post-Break fast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Pre-bed
Premixed Human Insulin BD	X		X		X		X
Premixed Insulin Analogue BD	X	X				X	
Premixed Insulin Analogue TDS	X	X		X		X	

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

To Control	Adjust
Pre-breakfast Glucose	Pre-bed intermediate/long-acting insulin or pre-dinner premixed.
2-hours Post-breakfast Glucose	Pre-breakfast rapid-acting or premixed insulin analogue.
Pre-lunch Glucose	Pre-breakfast short-acting or premixed human insulin.
2 hours Post-lunch Glucose	Pre-lunch rapid-acting or pre-lunch premixed insulin analogue.
Pre-dinner Glucose	Pre-lunch short-acting or pre-breakfast premixed human insulin.
Post-dinner/Pre-bed Glucose	Pre-dinner rapid-acting or pre-dinner premixed insulin.

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

Recommendations: Insulin Initiation, Optimisation and Intensification

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

SLIDE 22

Insulin Pump Therapy

- Continuous subcutaneous insulin infusion (CSII) 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

SLIDE 24

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.

SLIDE 25

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 m^2 (exenatide and lixisenatide) and e-GFR <60ml/min/1.73 m^2 (liraglutide).

SLIDE 26

Non-insulin Injectables - GLP1 - RA

Drug	Formulation	Minimum dose	Maximum dose
Exenatide IR	5 µg/20 µL 10 µg/40 µL	5 µg BD	10 µg BD
Exenatide XR	2 mg	2 mg weekly	2 mg weekly
Liraglutide	6 mg/mL	0.6 mg OD	1.8 mg OD
Lixisenatide	50 µg/mL 100 µg/mL	10 µg OD	20 µg OD

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

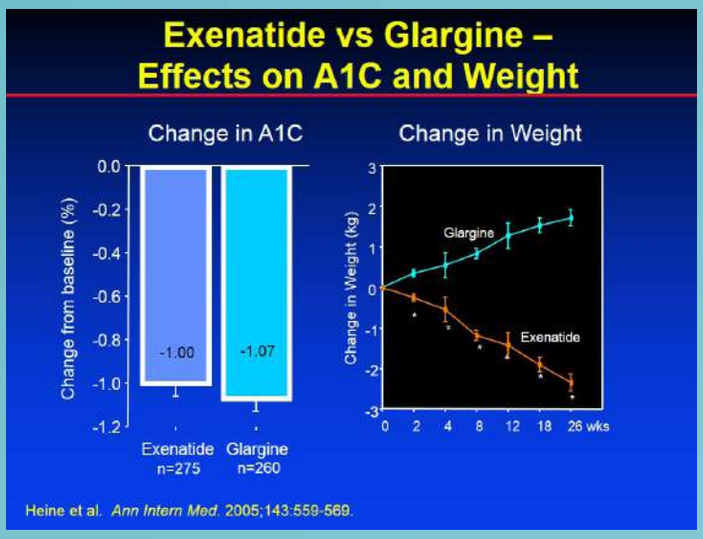
- Progressive weight loss is seen because of its effect on satiety and delay in gastric emptying.
- Main adverse effects are gastrointestinal symptoms, notably nausea which can be minimized by starting at a low dose with up-titration after a month
- It should be stored in the refrigerator (36 to 46°F [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

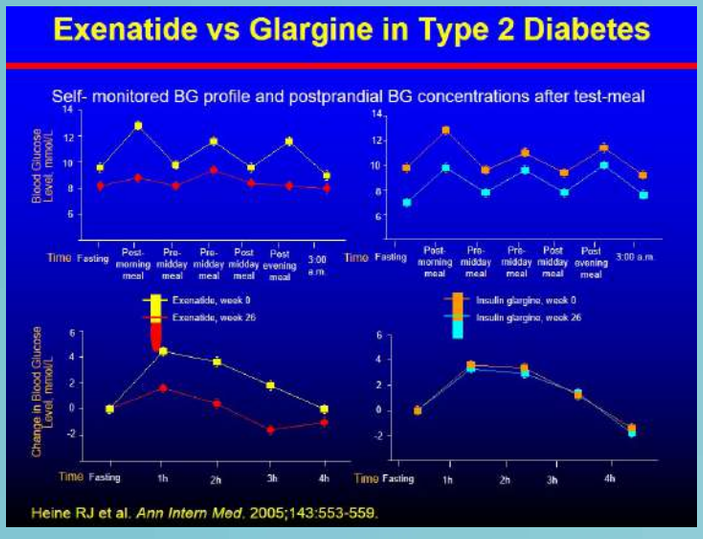
Liraglutide

- 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 0.6mg 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.

SLIDE 30



SLIDE 31



TOPIC

7

Case Study

insulin therapy & injectables

SLIDE 1

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

SLIDE 2

On Follow-up…

Weight 80 kg, BMI 32 kg/m^2, 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.

SLIDE 3

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.

SLIDE 4

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.

SLIDE 5

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.

SLIDE 6

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.

SLIDE 7

Case 3

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

Weight 83 kg, BMI 33 kg/m^2

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

SLIDE 8

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 NPDR bilateral

ALT 77 iu/L, US Liver: Fatty changes

Symptoms of OSA

SLIDE 9

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

SLIDE 10

Case 1

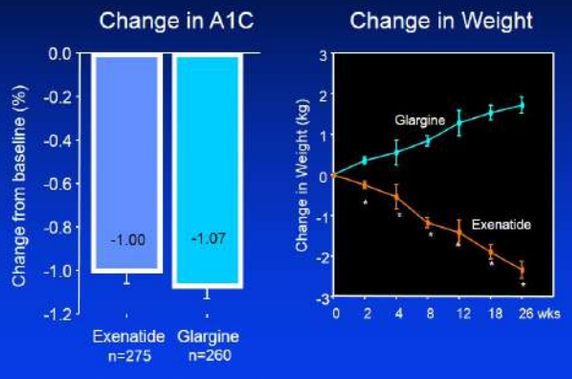
52 year old truck driver, night drives
DM2 3+ years, Smoker , BMI 38, BP 164/92
Current meds:
metformin, gliclazide, pioglitazone, lovastatin, perindopril
HbA1c 10.1%, FBG 11.8 mmol/l, Chol 5.3, TG 3.1, eGFR 67

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

SLIDE 11

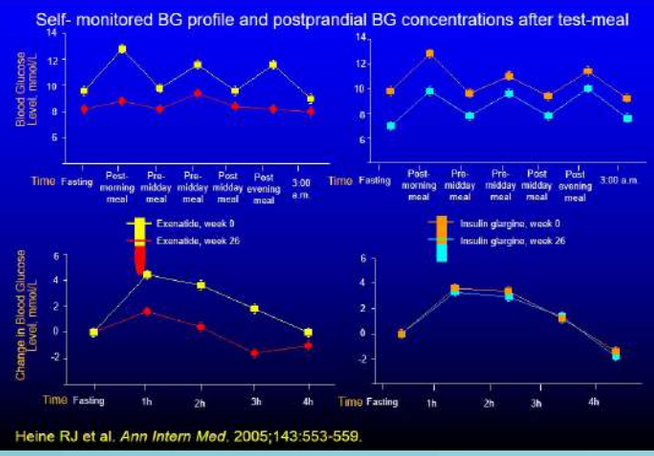
Exenatide vs Glargine – Effects on A1C and Weight



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

SLIDE 12

Exenatide vs Glargine in Type 2 Diabetes



Heine RJ et al. *Ann Intern Med.* 2005;143:553-559.

TOPIC

8

Lecture Notes

diabetes with hypertension

SLIDE 1

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

J. Hypertension '93 Mar;11(3):309-17
National Diabetes Registry 2009-2012

SLIDE 2

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

JNC 8: JAMA. 2014;311:507–520

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

SLIDE 3

Treatment Goals

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

ADVANCE ON: Nejm2014; 371:1392-1406
UKPDS: Br Med J 1998; 317: 703-713

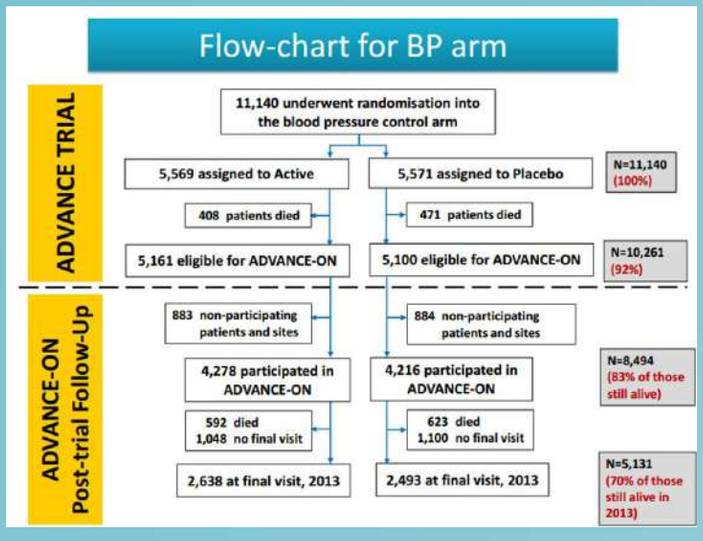
SLIDE 4

ADVANCE-ON

ADVANCE -
post trial **O**bservatio**N**al Study

BP Arm Results

SLIDE 5



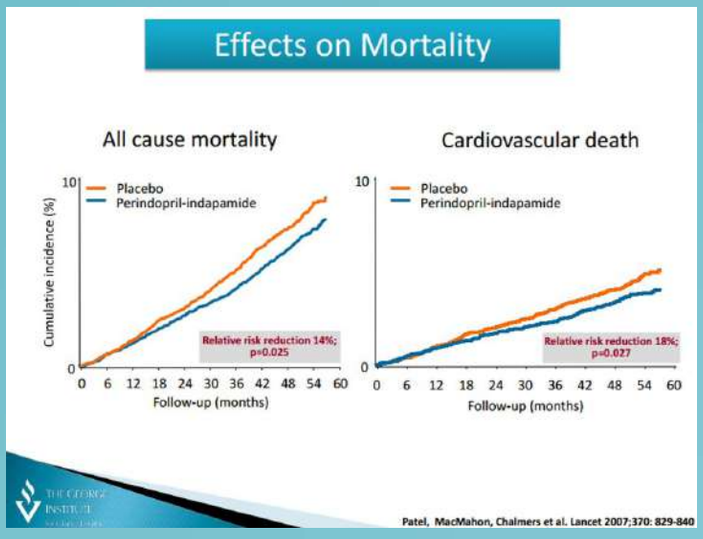
SLIDE 6

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

BP arm	BP level (mmHg) Mean	
	Active	Placebo
Pre-randomization	145/81	145/81
Last randomized visit (after median of 4.4 years)	136/74	140/75
First ADVANCE-ON visit (a further 2.9 years later)	137/75	137/75
Final ADVANCE-ON visit (a further 3 years later)	137/74	138/75

ADVANCE-ON

SLIDE 7



SLIDE 8

Management

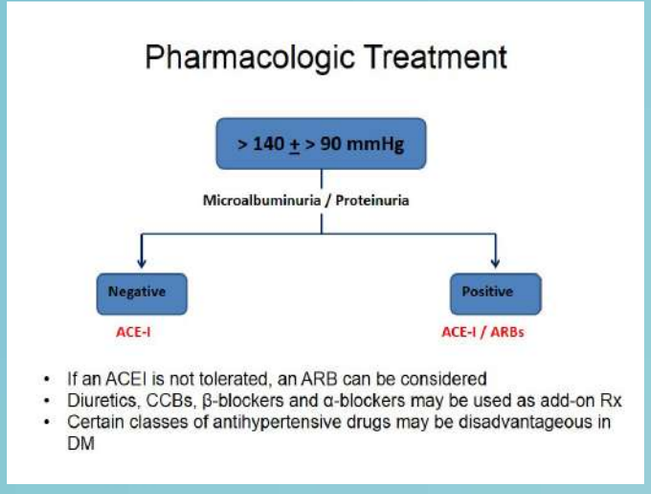
Non-Pharmacological Treatment

- Non-pharmacological management cannot be over emphasised.
- Dietary counselling
  - Target at optimal body weight
  - Consider glycaemia / dyslipidaemia control
- Dietary sodium restriction is advisable - enhances the effects of ACE-Is and ARBs.
- Further sodium restriction, + diuretic, may be necessary in nephropathy or when the BP is difficult to control.

JNC 8; JAMA. 2014;311:507–520

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.

SLIDE 9



SLIDE 10

Recommendations

- Pharmacological treatment should comprise a regimen that includes either an ACEI or an ARB as first line.
- ARBs have been reported to be superior to conventional non-ACE-inhibitors antihypertensive drugs
  - slowing the progression of nephropathy at the microalbuminuric and overt nephropathy stages.

ESH. Eur Heart J. 2013;34:2159–2219.
ASH . J Hypertens. 2014;32:3–15.

SLIDE 11

Recommendations

- Multiple drug therapy is generally required to achieve blood pressure targets.
- Diuretics, calcium channel blockers (CCBs), beta-blockers and peripheral alpha-blockers may be used as add-on therapy.
- One or two antihypertensive medications should be administered at bedtime
  - There is evidence that taking at least one antihypertensive medication at bedtime reduce risk of CVD events.
- In pregnant individuals with diabetes and hypertension, recommended BP target goals should be 110-129/65-79 mmHg

DiabCare 2011; 34: 1270-1276

90% of patients require three antihypertensive medications to achieve target.

SLIDE 12

Table 8 (A): Choice of antihypertensive drugs in diabetes patients with concomitant conditions (Adapted from Malaysian CPG for Hypertension 2008)

Concomitant Disease	Diuretics	β-blockers	ACEIs	CCBs	Peripheral α-blockers	ARBs
DM (without nephropathy)	+	+/-	+++	+	+/-	++
DM (with nephropathy)	++	+/-	+++	++*	+/-	+++
Gout	+/-	+	+	+	+	+
Dyslipidaemia	+/-	+/-	+	+	+	+
Coronary heart disease	+	+++	+++	++	+	+
Heart failure	+++	+++#	+++	+@	+	+++

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

+/- Use with care
- Contraindicated
* Only non-dihydropyridine CCBs

Metoprolol, bisoprolol, carvedilol – dose needs to be gradually titrated
@ Current evidence available for amlodipine and felodipine only

SLIDE 13

Table 8 (B): Choice of antihypertensive drugs in diabetes patients with concomitant conditions (Adapted from Malaysian CPG for Hypertension 2008)

Concomitant Disease	Diuretics	β-blockers	ACEIs	CCBs	Peripheral α-blockers	ARBs
Asthma	+	-	+	+	+	+
Peripheral vascular disease	+	+/-	+	+	+	+
Non-diab renal impairment	++	+	+++	+*	+	++
Renal artery stenosis	+	+	++$	+	+	++$
Elderly with no co-morbid conditions	+++	+	+	+++	+/-	+

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

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

SLIDE 14

Summary

- Multi factorial approached 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.

TOPIC

8

Case Study

diabetes with hypertension

SLIDE 1

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.

SLIDE 2

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?

SLIDE 3

- 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)

SLIDE 4

On examination:

- Obese
- Weight 98 kg, BMI 35 kg/m^2
- BP 160/90 mmHg
- PR 88 beats/minute
- Bilateral proliferative retinopathy
- Minimal bilateral leg oedema
- Other systemic examination: unremarkable

SLIDE 5

Investigation results:

• A1c	9.2 %
• FBS	11.8 mmol/L
• Creatinine	106 µmol/L
• e-GFR	88 ml/min/1.73 m^2
• 24h urinary protein	200 mg/24h
• ECG	LVH

SLIDE 6

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)

SLIDE 7

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?

SLIDE 8

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

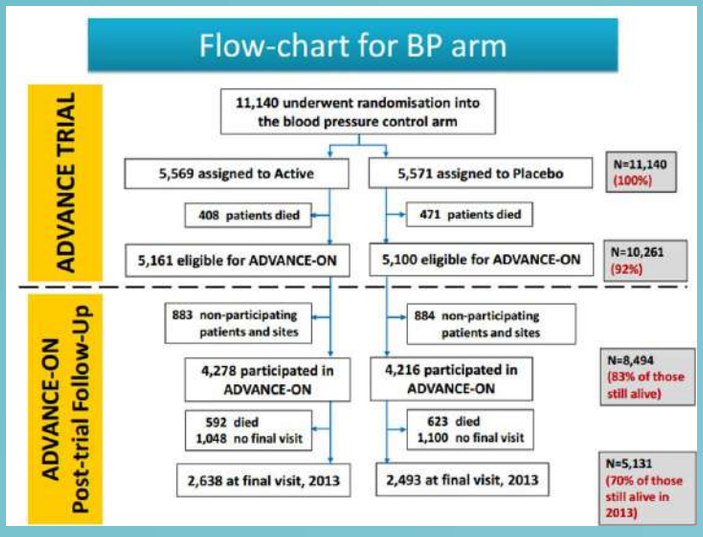
SLIDE 9

ADVANCE-ON

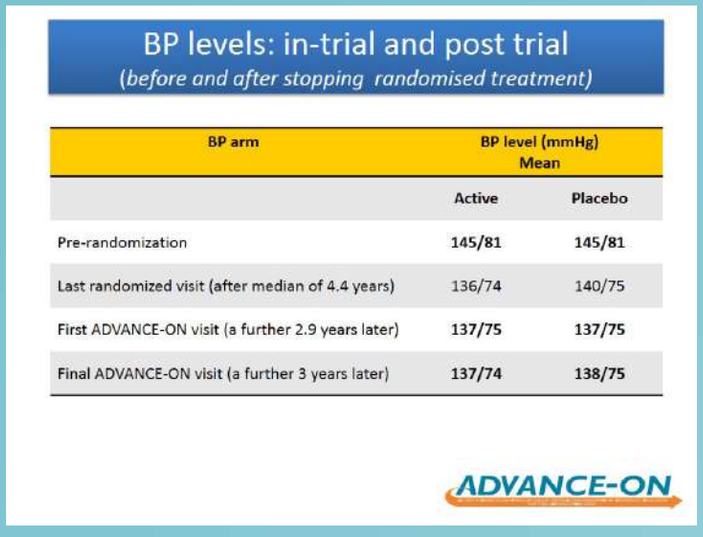
ADVANCE -
post trial **O**bservatio**N**al Study

BP Arm Results

SLIDE 10



SLIDE 11



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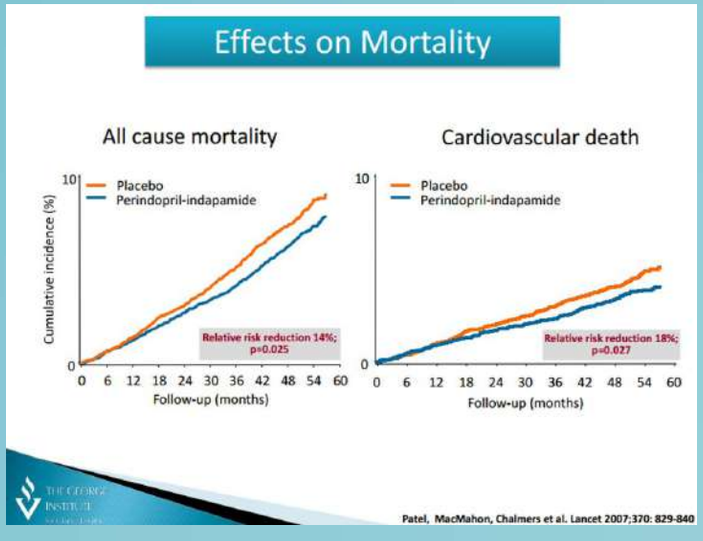
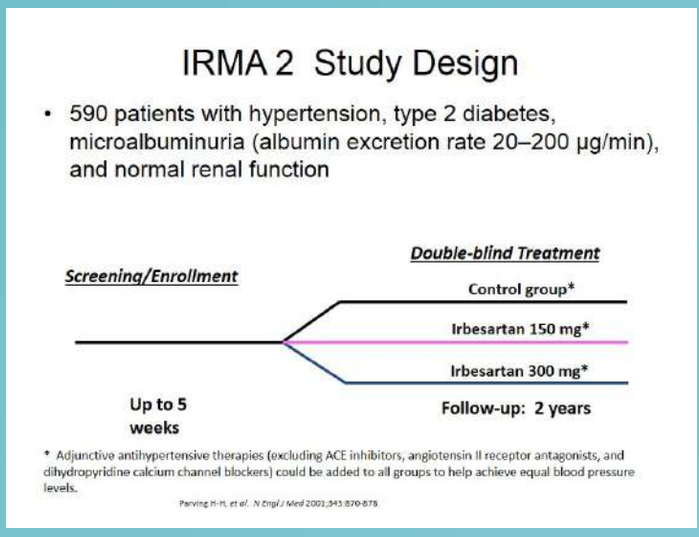
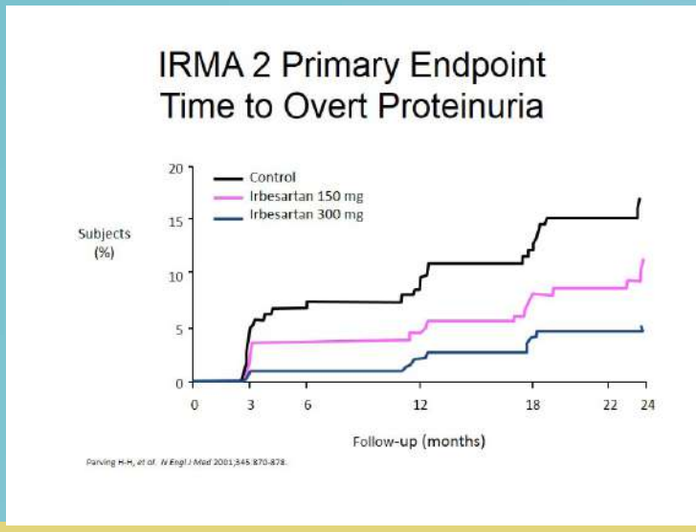
SLIDE 12



SLIDE 13



SLIDE 14

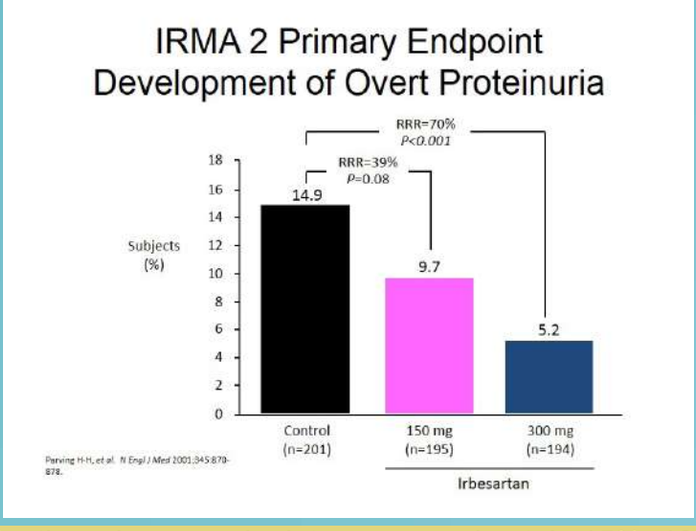


IRMA 2 is a positive study, demonstrating a 70% risk reduction for the primary endpoint (prevention or slowing of progression to overt diabetic nephropathy), independent of the effects of irbesartan on systemic blood pressure.

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).

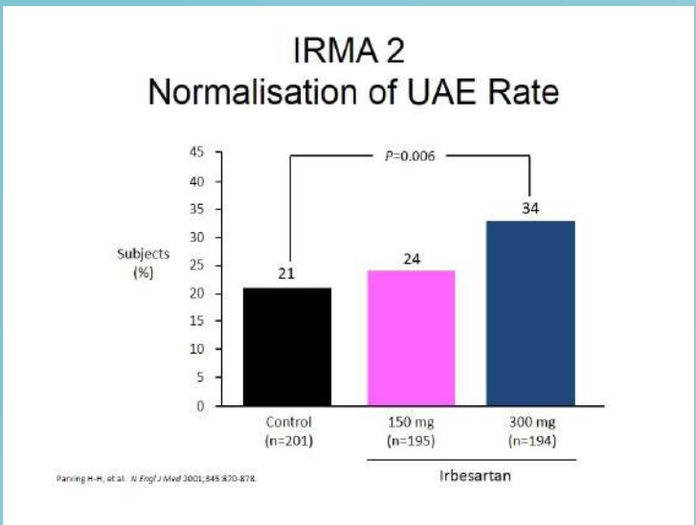
SLIDE 15



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.

SLIDE 16



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).

SLIDE 17

Table 8 (A): Choice of antihypertensive drugs in diabetes patients with concomitant conditions (Adapted from Malaysian CPG for Hypertension 2008)

Concomitant Disease	Diuretics	β-blockers	ACEIs	CCBs	Peripheral α-blockers	ARBs
DM (without nephropathy)	+	+/-	+++	+	+/-	++
DM (with nephropathy)	++	+/-	+++	++*	+/-	+++
Gout	+/-	+	+	+	+	+
Dyslipidaemia	+/-	+/-	+	+	+	+
Coronary heart disease	+	+++	+++	++	+	+
Heart failure	+++	+++#	+++	+@	+	+++

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

+/- Use with care
- Contraindicated
* Only non-dihydropyridine CCBs

Metoprolol, bisoprolol, carvedilol – dose needs to be gradually titrated
@ Current evidence available for amlodipine and felodipine only

SLIDE 18

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.

TOPIC

9

Lecture Notes

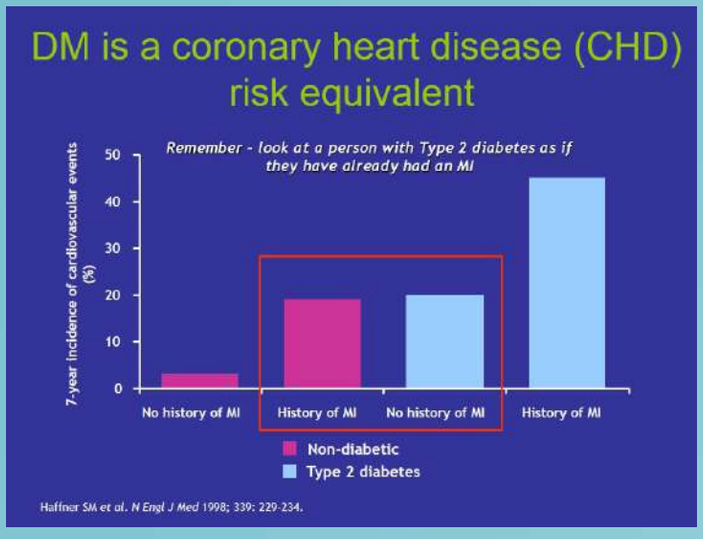
diabetes with dyslipidaemia

SLIDE 1

Introduction

- 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.
- Efforts must be directed to control other risk factors such as dyslipidaemia, hypertension and other new emerging risk factors

SLIDE 2



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.[1]

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 can 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
Haffner SM *et al. N Engl J Med* 1998; 339: 229–234.

SLIDE 3

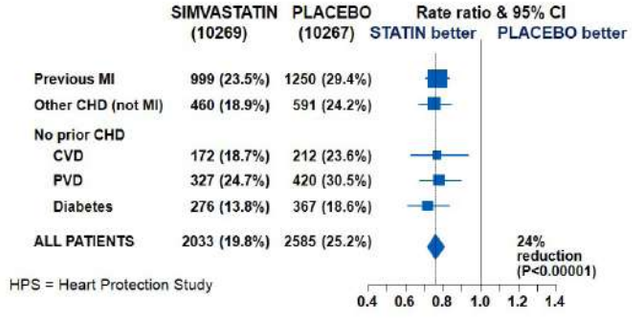
Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of Complication
Blood glucose control	Heart attack	↓ 37%[1]
Blood pressure control	Cardiovascular disease	↓ 51%[2]
	Heart failure	↓ 56%[3]
	Stroke	↓ 44%[3]
	Diabetes-related deaths	↓ 32%[3]
Lipid control	Coronary heart disease mortality	↓35%[4]
	Major coronary heart disease event	↓55%[5]
	Any atherosclerotic event	↓37%[5]
	Cerebrovascular disease event	↓53%[4]

[1] UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.
[2] Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[3] UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[4] Grover SA, et al. *Circulation*. 2000;102:722-727.
[5] Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.

SLIDE 4

HPS: Statin Therapy Beneficial Among Patients with Diabetes



HPS = Heart Protection Study

HPS *Lancet* 2002;360:7-22

SLIDE 5

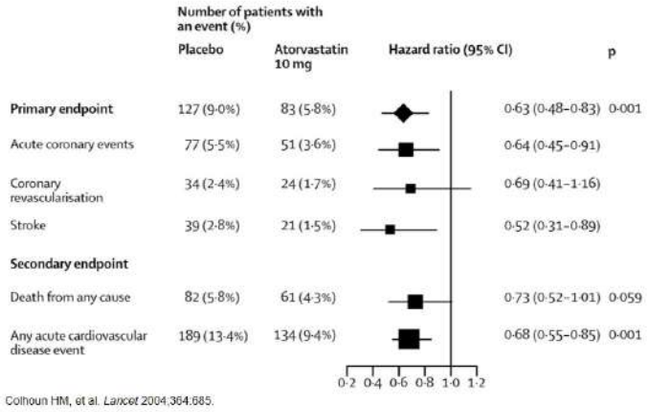
CARDS: Effect of Statin for PRIMARY Prevention in DM

- 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

Colhoun HM, et al. *Lancet* 2004;364:685

SLIDE 6

CARDS: Statins Reduced CVD in Patients with DM



Colhoun HM, et al. *Lancet* 2004;364:685.

SLIDE 7

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.

SLIDE 8

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%

HPS *Lancet* 2002;360:7-22
Colhoun HM, et al. *Lancet* 2004;364:685

SLIDE 9

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

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

NNT= number needed to treat

Yudkin JS et al. Diabetologia 53:2079–2085, 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

Non-HDL cholesterol	< 3.4 mmol/L (when TG > 2.3 mmol/L)
HDL cholesterol	> 1.0 mmol/L for males > 1.2 mmol/L for females
TG	< 1.7 mmol/L

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

Lipid Goal	**Initial Drug**	**Suggested addition (in order of preference)**
Lower LDL cholesterol	Statins	Ezetimibe
Increase HDL cholesterol	Fibrates	-
Lower TG	Fibrates or nicotinic acid	Statins
Treat combined hyperlipidaemia	Statins	Fibrates Resin plus Fibrates Nicotinic Acid

SLIDE 15

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 ezitimibe 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.

SLIDE 16

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.

SLIDE 17

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.

TOPIC

9

Case Study

diabetes with dyslipidaemia

SLIDE 1

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

SLIDE 1

On examination:

Weight 74 kg; Height: 1.67 m, BMI: 27.9 kg/m^2

BP 130/80 mmHg. Haemodynamically stable.

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

SLIDE 3

Investigation results:

Creatinine 92 umol/L, e-GFR >60 ml/min/1.73 m^2

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

SLIDE 4

What should be next course of action?

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

SLIDE 5

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

TOPIC

10

Lecture Notes

diabetes with obesity

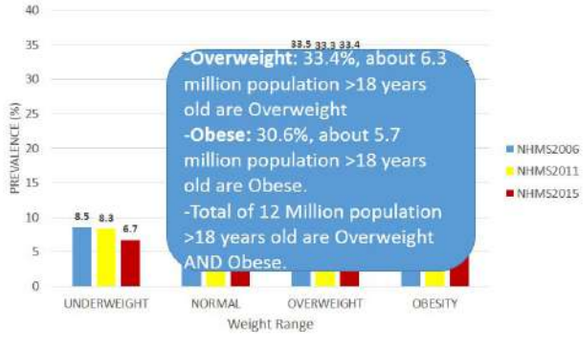
SLIDE 1

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

SLIDE 2

PREVALENCE OF NUTRITIONAL STATUS, ≥ 18 YEARS, NHMS III (2006), NHMS 2011 AND NHMS 2015 (CPG 2004)



Prevalence of Overweight and Obesity among adults age >18 years and above from latest NHMS 2015. BMI used According to Malaysia CPG 2004.

SLIDE 3

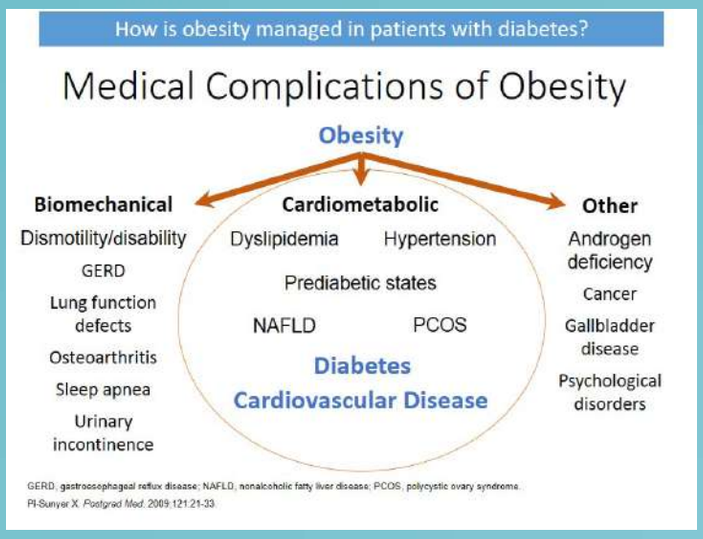
Classification of Weight By BMI

The initial assessment of people with diabetes should include height, weight, BMI (kg/m2) and waist circumference

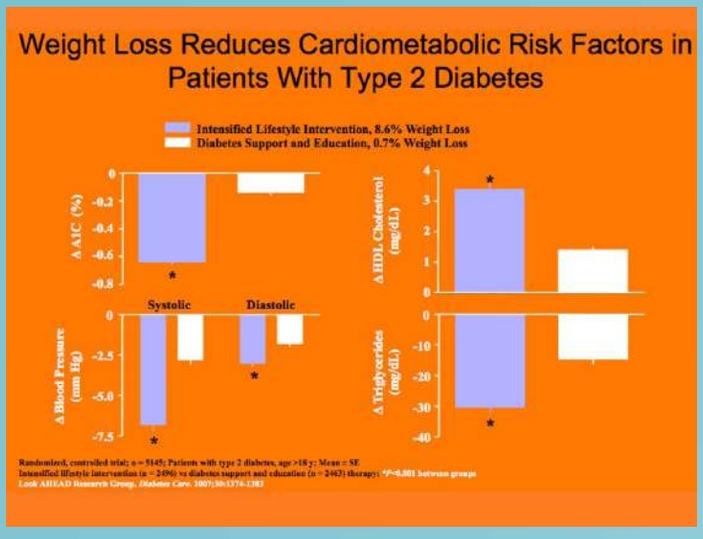
Classification	BMI (kg/m2)	**Risk of co-morbidities (T2DM, HPT, CVD)
Underweight	< 18.5	Low (but increased risk of other clinical problems)
Normal	18.5 – 22.9	Optimal
Overweight:	BMI ≥ 23.0	
Pre-Obese	23.0 – 27.4	Increased
Obese I	27.5 – 34.9	High
Obese II	35.0 – 39.9	Very high
Obese III	≥ 40	Extremely high

4

SLIDE 4



SLIDE 5



SLIDE 6

Anti-Diabetic Agents and Their Effects on Weight

Weight Gain	Weight Neutral	Weight Reduction
Insulin	Metformin	GLP-1 RA
TZDs	AGI	SGLT 2 Inhibitors
Sulphonylureas	DPP-4 Inhibitors	
Meglitinides		

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.

SLIDE 7

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.

SLIDE 8

Pharmacotherapy for Obesity

When to start Anti Obesity?

- Diabetic patients with BMI of ≥ 27.0 kg/m2 and failed 6 months of life style modifications.

SLIDE 9

Anti Obesity Agents Indicated for Use In Diabetes

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

In Malaysia, 2 anti-obesity agents have been approved, Phentermine and Orlistat. Phentermine only indicated for short term-3 months.

SLIDE 10

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/m^2
  - Diabetic patients > 30 kg/m^2 with 1 or more features of metabolic syndrome.

SLIDE 11

Criteria for Bariatric Surgery

Factor	Criteria
Weight Loss History	Failure of previous nonsurgical attempts at weight reduction, including nonprofessional programs eg weight watchers)
Commitment	Expectation that patient will adhere to postoperative care •Follow up visits with healthcare team. •Compliance to medical management. •Continued dietary restrictions.
Exclusion criteria	•BMI<30kg/m^2. •Current drug or alcohol abuse •Uncontrolled, severe psychiatric illness •Lack of comprehension of risks, benefits, expected outcomes, alternatives and required lifestyle changes.

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.

TOPIC

10

Case Study

diabetes with obesity

SLIDE 1

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 natrilix 1 tab OD)
Hyperlipidemia (20 mg rosuvastatin)
Snores heavily and being investigated for sleep apnea by respi. unit

SLIDE 2

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

SLIDE 3

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

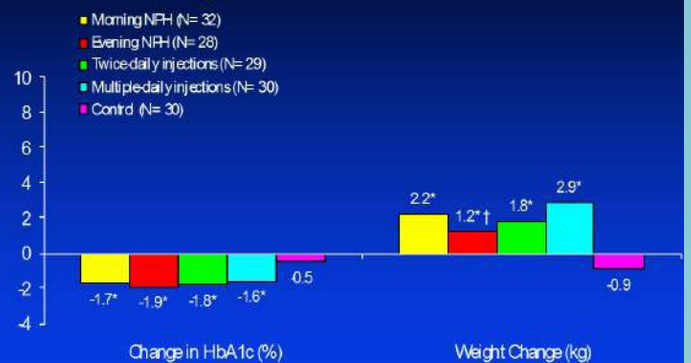
SLIDE 4

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

SLIDE 5

Comparison of Insulin Regimens Among Oral Treatment Failures



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

Yki-Jarvinen H, et al. *N Engl J Med*. 1992;327:1426-1433.

SLIDE 6

Case 1 (2 months later)

He was finally convinced to start on bedtime insulatard 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

SLIDE 7

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]
b. Mitchell NS, et al. *Psychiatr Clin North Am.* 2011;34:717-732.[30]

SLIDE 8

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
  - β-blockers

a. National Institutes of Health.[21]
b. Leslie WS, et al. *QJM.* 2007;100:395-404.[34]

SLIDE 9

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.[21]

SLIDE 10

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.
Vallis M, et al. *Can Fam Physician*. 2013;59:27-31.[26]

SLIDE 11

Assessing Patient Readiness and Resources

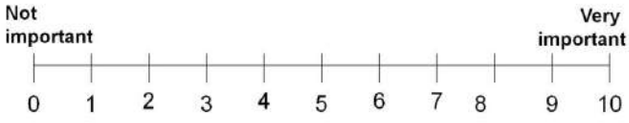
- Reasons and motivation for weight loss
- Potential barriers to adopting change
- Time availability
- Understanding of risks and benefits
- Support expected from family and friends
- Weight loss goals

National Institutes of Health.[21]

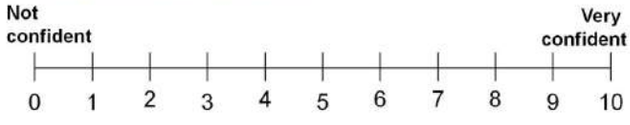
SLIDE 12

Assessing Patient Readiness for Weight Loss

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



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



SLIDE 13

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

National Institutes of Health.[21]

SLIDE 14

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?

SLIDE 15

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

SLIDE 16

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

SLIDE 17

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)

SLIDE 18

Selecting Treatment for Obesity

Treatment	BMI Category					
	< 24.9	25-26.9	27-29.9	30-35	35-39.9	>40
Diet, exercise, behavior therapy	With co-morbidities	With co-morbidities	+	+	+	
Pharmacotherapy			With co-morbidities	+	+	+
Surgery					With co-morbidities	+

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

SLIDE 19

A Guide to Selecting Treatment

Body Mass Index category

Treatment	25-26.9	27-29.9	30-34.9	35-39.9	≥40
Diet, physical activity, and behavior therapy	With co-morbidity	+	+	+	+
Pharmacotherapy		With co-morbidity	+	+	+
Surgery				With co-morbidity	+

NIH The Practical Guide. 2000 http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437739.71477.ee.citation

SLIDE 20

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

TOPIC

11

Lecture Notes

management of diabetic emergencies 1

SLIDE 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.

2

SLIDE 2

Symptoms of Hypoglycaemia

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

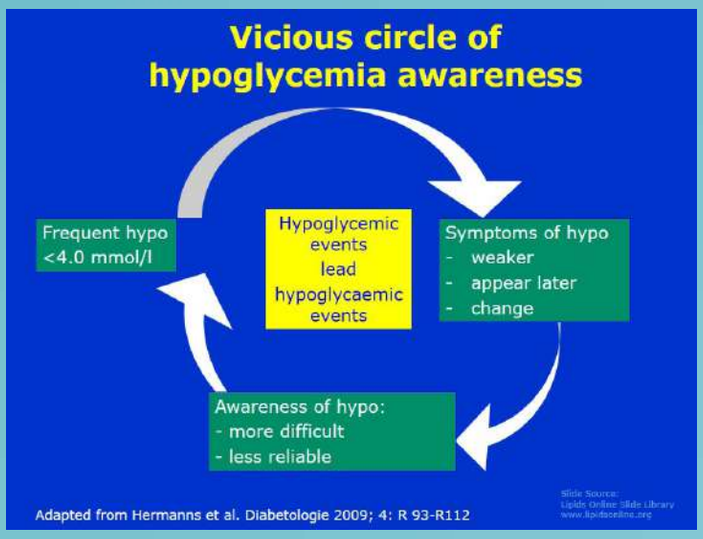
3

SLIDE 3

Severity of Hypoglycaemia

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

SLIDE 4



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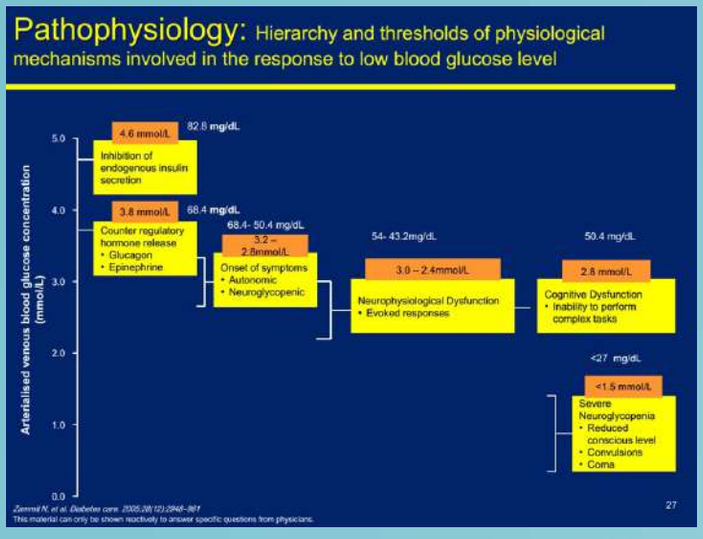

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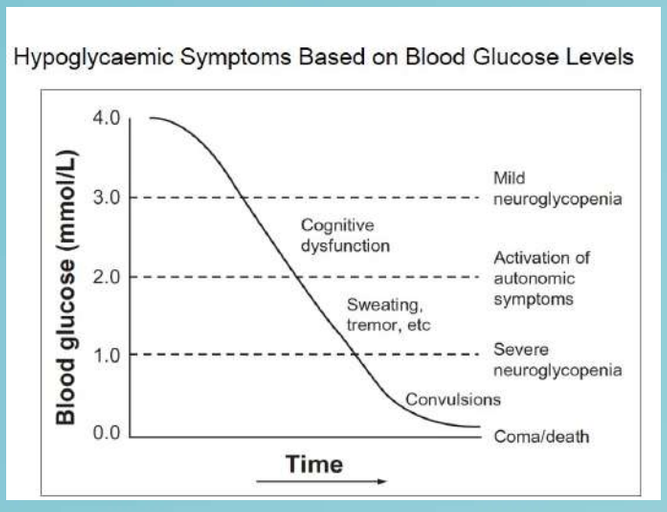
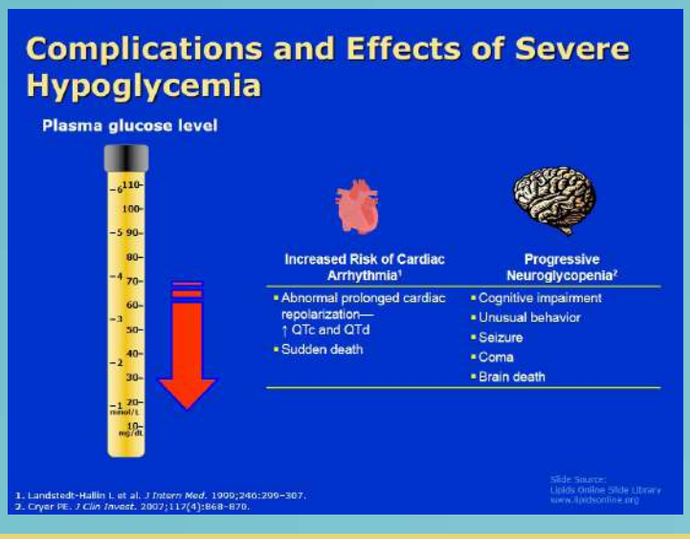


SLIDE 7



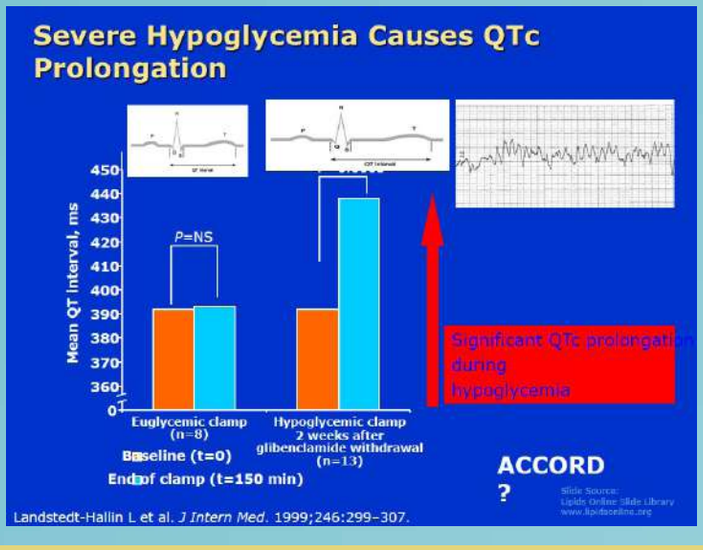
Complications and Effects of Severe Hypoglycemia

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]

SLIDE 8



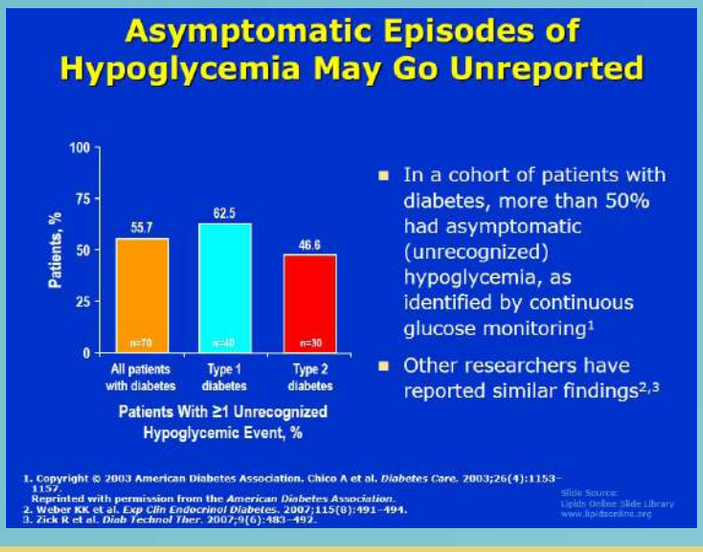
Severe Hypoglycemia May Cause a Prolongation of QT Interval in Patients With Type 2 Diabetes

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

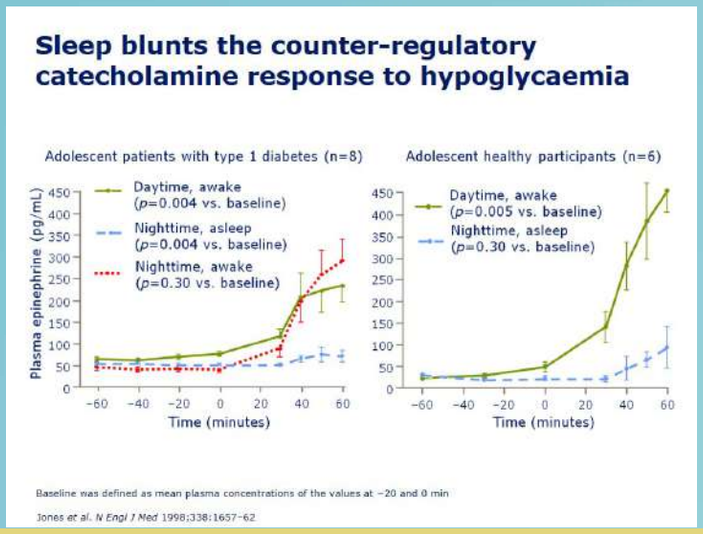
euglycaemic clamp study after an additional 3 to 4 months.[1]
As demonstrated in the graph, the study showed that mean QT intervals and QT dispersion were significantly prolonged after the hypoglycaemic clamps. These results showed that hypoglycaemia affected repolarization of the myocardium, creating 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]

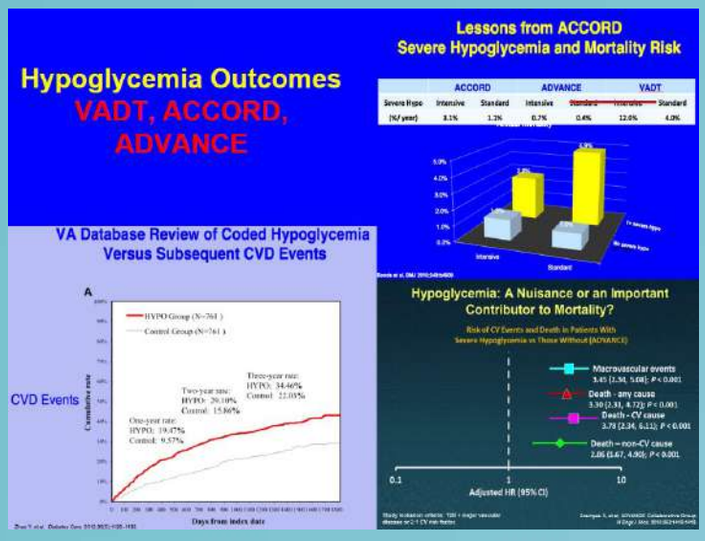
SLIDE 10



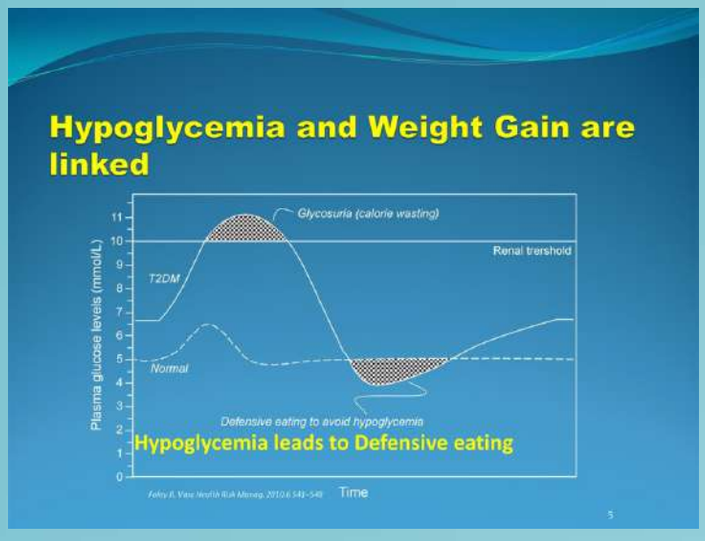
Sleep decreases the epinephrine response to hypoglycaemic events in patients with T1DM and the warning signs of hypoglycaemia are reduced.
Jones study: Epinephrine response was measured in adolescents with T1DM (n=8) and age-matched controls (n=6) in daytime and nighttime in response to insulin-induced 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



SLIDE 12



SLIDE 13

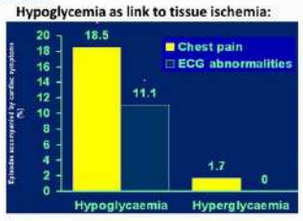
Hypoglycaemia in T2DM:

A possible link to increased CV risk/events

POSSIBLE MECHANISMS:

- **Haemodynamic changes:**
  - activation of autonomic nervous system
  - 10-50 fold increased secretion of adrenaline & noradrenaline
- **ECG changes:**
  - longer QT interval
  - hypokalemia
- **Haemorheological changes:**
  - platelet activation
  - increased viscosity

Hypoglycemia as link to tissue ischemia:



***P <0.01 vs episodes during hyperglycaemia and normoglycaemia.BGL=blood glucose level; T2DM=type 2 diabetes mellitus.**

Study of 72-h continuous glucose monitoring and simultaneous cardiac Holter monitoring in patients with T2DM treated with insulin and history of frequent hypoglycaemia and coronary artery disease (n=19). 54 episodes of hypoglycaemia reported (BGL <3.9 mmol/L)

Desouza C, et al. *Diabetes Care*. 03; 26: 1485–1489.

- **Symptoms of Hypoglycemia : ↑ 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]**Cryer PE. *Diabetologia*. 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.

SLIDE 16

Treatment of SEVERE Hypoglycemia in Unconscious Person with IV Access

1. **Treat** with 10-25 g (20-50 cc of D50W) of glucose intravenously over 1-3 minutes
2. **Retest** in 15 minutes to ensure the BG >4.0 mmol/L and retreat with a further 15 g of carbohydrate if needed
3. Once conscious, **eat** usual snack or meal due at that time of day or a snack with 15 g carbohydrate plus protein

SLIDE 17

Examples of 15 g Simple Carbohydrate

- 15 g of glucose in the form of glucose tablets 
- 15 mL (3 teaspoons) or 3 packets of sugar dissolved in water 
- 175 mL (3/4 cup) of juice or regular soft drink 
- 6 Lifesavers (1=2.5 g of carbohydrate)
- 15 mL (1 tablespoon) of honey 

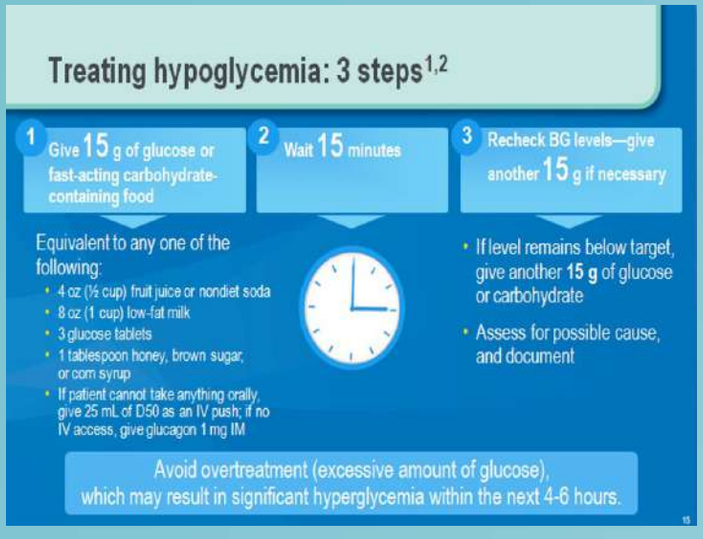
Evidence suggests that 15 g of glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people.

SLIDE 18

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.

SLIDE 19



SLIDE 20

- 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

SLIDE 21

- 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.

TOPIC

11

Case Study

management of diabetic emergencies 1

SLIDE 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.

SLIDE 2

Case 1

- In the afternoon the patient was found comatose in bed.
- What is the possible reason for her unconsciousness?
- What would you do?

SLIDE 3

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).

SLIDE 4

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.

SLIDE 5

Case 1

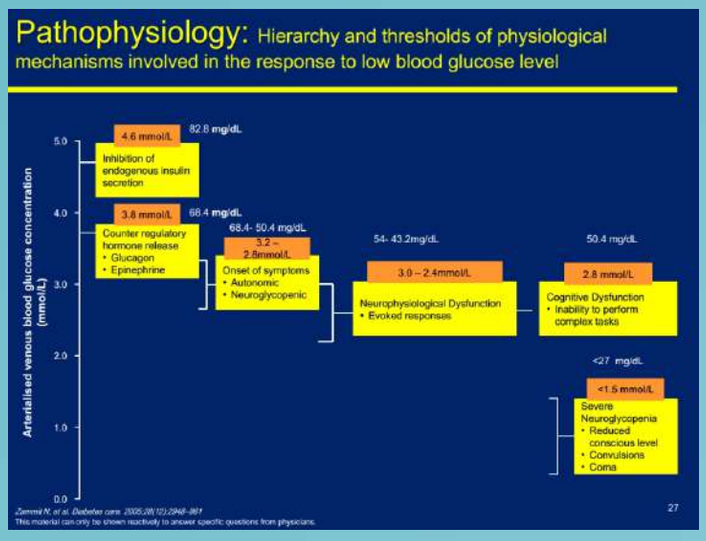
- Blood glucose should have been closely monitored in the hospital and, if it was low, intravenous glucose infusion should have begun.
- In addition, every unconscious patient should be considered as hypoglycaemic, especially if the patient has diabetes, until immediate estimation of the blood glucose 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.

SLIDE 6

Case 1

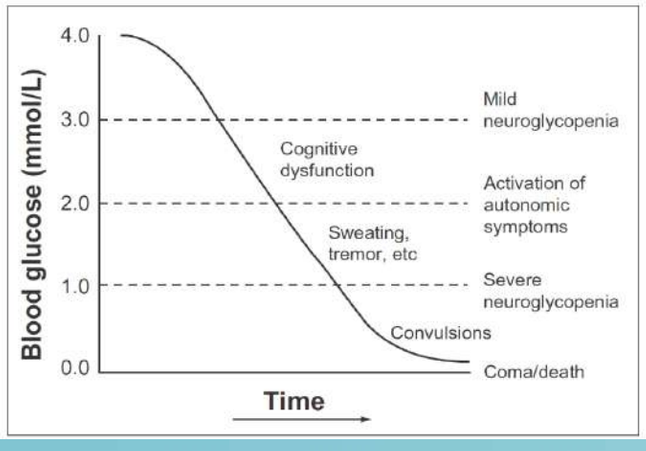
- How will you manage this patient?
- The patient was unconscious, thus a bolus of 20-50 ml of 50% glucose solution or 50 ml of 35% glucose solution, followed by infusion of 10-20% glucose solution should begin with frequent monitoring of blood glucose.

SLIDE 7



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

TOPIC

12

Lecture Notes

management of diabetic emergencies 2

SLIDE 1

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

SLIDE 2

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

SLIDE 3

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

SLIDE 4

Principles Of Management – 1st Hour

1st Hour: Immediate Management

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

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

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

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

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

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

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

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

SLIDE 5

Fluid And Potassium Replacement

Initial Fluid & Potassium Replacement

Restoration of circulating volume is a priority

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

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

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

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

Potassium replacement:

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

Caution:
Withold potassium replacement if no urine output.

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

SLIDE 6

2-6th Hour

2nd - 6th Hour

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

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

Step 8 Continue fluid replacement via infusion pump as follows:
- 1000 mL of 0.9% saline with potassium chloride over next 2 hours
- 1000 mL of 0.9% saline with potassium chloride over next 4 hours
- Once blood glucose falls below 14 mmol/L:
  - Switch to 5% dextrose at 125 mL/hr and reduce insulin infusion rate to 0.05 units/kg/hour; or
  - Switch to 10% dextrose at 125 mL/hr with no change in insulin infusion rate.

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

Step 9. Assess response to treatment

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

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

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

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

SLIDE 7

12-24 Hours

12-24 hours

By 24 hours the ketonaemia and acidosis should have resolved.

Aim:

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

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

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

If DKA resolved go below

SLIDE 8

Resolution Of DKA

Resolution of DKA

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

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

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

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

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

SLIDE 9

What is the next step of management?

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

- If DKA is not resolved identify and treat the reasons for failure to respond
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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

TOPIC

12

Case Study

management of diabetic emergencies 2

SLIDE 1

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 gliclazide 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.

SLIDE 2

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

SLIDE 3

Laboratory Results

Urinalysis:

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

Venous blood gas:

- pH of 7.06, pCO_2 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 5.0 mmol/L, chloride of 112 mmol/L, creatinine 136 µmol/L

FBC:

- Leucocyte 23 x 10^9/L with predominant neutrophils, haematocrit 55%

SLIDE 4

Imaging

Chest X-ray: unremarkable

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

SLIDE 5

More tests?

Serum osmolality	Anion gap	Others
Formula : (2 x serum [Na]) + [glucose] + [urea] (all in mmol/L) Or **laboratory measured value**	($[Na^+] + [K^+]$) – ($[Cl^-] + [HCO_3^-]$)	**Septic workup** Pus – for culture and sensitivity Blood cultures
(2 x [142]) + [30] + [12] = **326** Normal range 275-295 mosmol/kg	(142 + 5) – (112 + 5.6) = **29.4** Normal range 8 – 16 mmol/L	ECG

SLIDE 6

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	This patient
• Infection • Missed insulin therapy • Acute coronary syndrome • CVA • Surgery	• Infection of left foot • Missed insulin therapy

SLIDE 8

What happen if treatment is delayed?

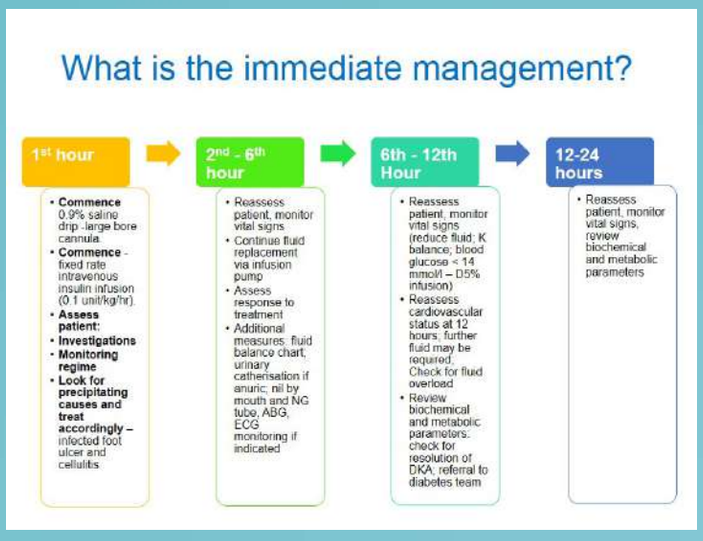
- High mortality rate:
  - Overall mortality is <1%
  - Mortality rate >5% in the elderly

SLIDE 9

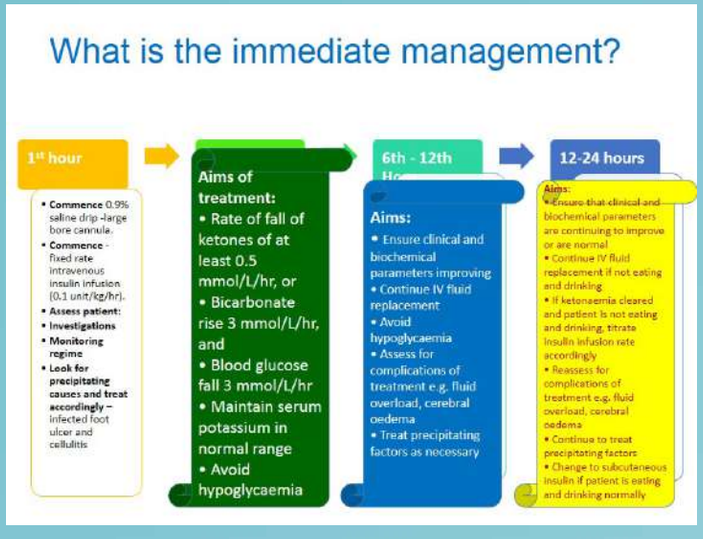
Prognosis

- Excellent with prompt treatment
- High-dependency unit (HDU) care

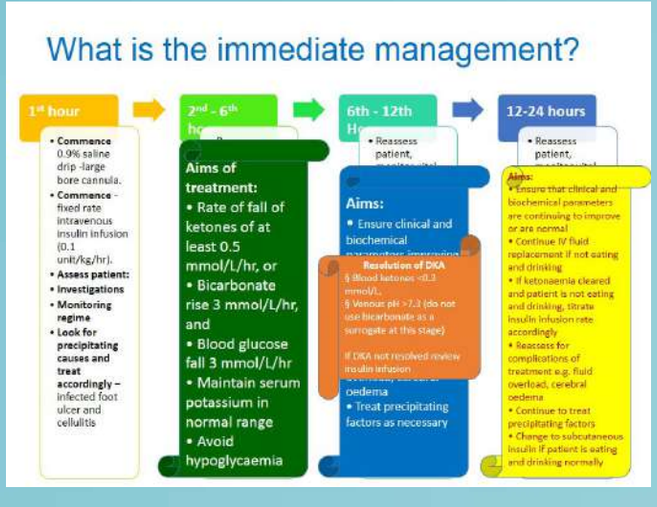
SLIDE 10



SLIDE 11



SLIDE 12



TOPIC

12

Lecture Notes

management of diabetic emergencies 2

SLIDE 1

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.

SLIDE 2

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

SLIDE 3

Diagnostic Criteria of HHS

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

SLIDE 4

Other Important Clinical Features

- There is **NO** significant hyperketonaemia (<3.0 mmol/L) or acidosis (pH >7.3, bicarbonate >15 mmol/L).
- When acidosis is present, causes of acidosis such as lactic acid and toxicology screen need to be investigated.
- The presence of acute cognitive impairment may be associated with:
  - cerebral oedema in severe cases or
  - significant electrolyte disturbances,
  - hyperosmolality (>330 mosmol/kg),
  - sudden drop in osmolality,
  - severe dehydration,
  - infection and sepsis,
  - hypoglycaemia during treatment
  - renal failure.

SLIDE 5

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.

SLIDE 6

Precipitating Factors For HHS

a) Infections and sepsis

b) Thrombotic stroke

c) Intracranial haemorrhage

d) Silent myocardial infarction

e) Pulmonary embolism

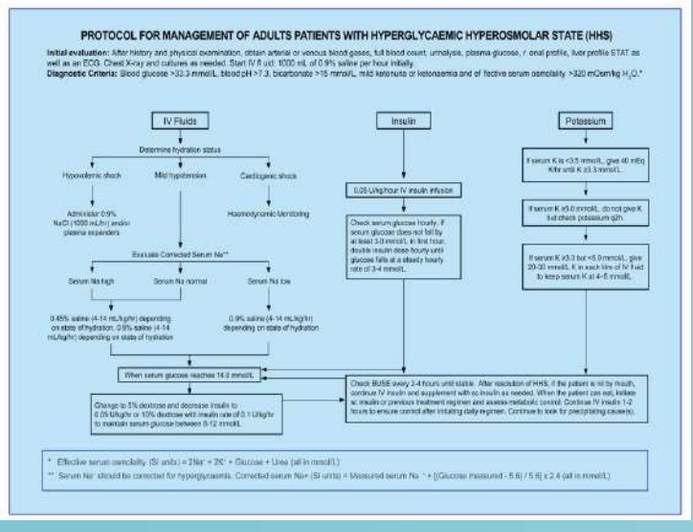
SLIDE 7

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

SLIDE 8



SLIDE 9

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.

SLIDE 10

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-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.

SLIDE 11

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.

TOPIC

12

Case Study

management of diabetic emergencies 2

SLIDE 1

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.

SLIDE 2

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: Hi

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.

SLIDE 3

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 176 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 10^9/L (80% polymorphonuclears), hematocrit and platelet counts were normal

C-reactive protein: 134 mg/L (normal < 5)

ESR 85 mm/1st hour

SLIDE 4

Investigation results

ECG

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

CXR:

- Consolidation right lower zone

SLIDE 5

More tests?

Serum osmolality	Anion gap	Others
Formula : (2 x serum [Na]) + [glucose] + [urea] (all in mmol/L) Or **laboratory measured value**	($[Na^+] + [K^+]$) – ($[Cl^-] + [HCO_3^-]$)	**Septic workup** Urine for culture and sensitivity Blood culture
(2 x [154]) + [59.8] + [14.6] = **382.4** Normal range 275-295 mosmol/kg	(154 + 5.4) – (110 + 20) = **69.4** Normal range 8 – 16 mmol/l	**Stroke workup** Including swallowing test and CT brain

SLIDE 6

What is the diagnosis?

This patient	• **Dehydration** - tachycardia, bp 84/52, dry mucosa and diminished skin turgor, confusion • **Blood glucose 59.8 mmol/l** • Urine ketones minimal • Bicarbonate 20 mmol/l – no acidosis
Criteria for Hyperglycaemic Hyperosmolar State	• Hypovolemia – dehydration • Marked hyperglycaemia > 33.3 mmol/l • pH > 7.3, bicarbonate > 15 mmol/l • Urine or blood ketones nil or minimal • Serum osmolality > 320 mOsm/kg
Diagnosis	• **Hyperglycaemic Hyperosmolar State**

SLIDE 7

What are the precipitating factors?

Precipitating factors	This patient
• Infection and sepsis • Thrombotic stroke • Intracranial haemorrhage • Silent myocardial infarction • Pulmonary infarction	• Stroke

SLIDE 8

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

SLIDE 9

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

SLIDE 10

What is the immediate management?

- Hydration
- Insulin
- Electrolytes balance

SLIDE 11

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

SLIDE 12

Insulin

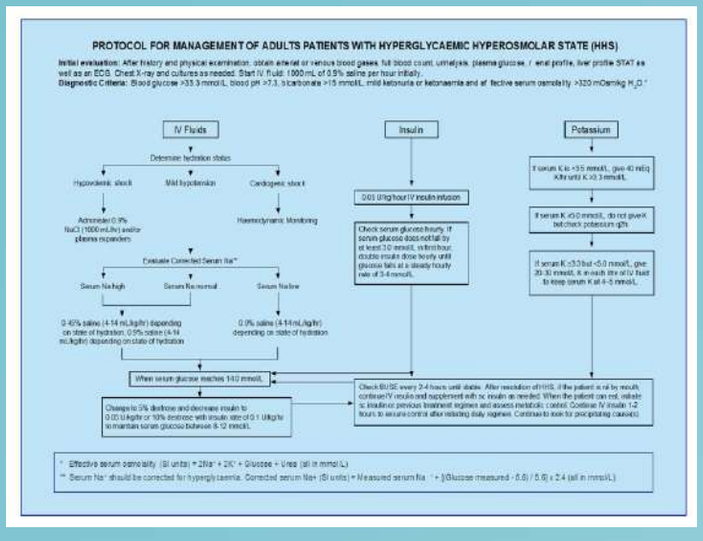
- Low dose IV insulin (0.05 units/kg/hr) commenced once blood glucose is no longer falling with IV fluids alone or immediately if there is significant ketonaemia (β-hydroxy butyrate >3 mmol/L).
- Prophylactic low molecular weight heparin (LMWH) is recommended unless contraindicated.

SLIDE 13

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.

SLIDE 14



TOPIC

13

Lecture Notes

management of chronic complications 1

SLIDE 1

Overview

Microvascular Complications:

- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular Complications:

- Coronary Heart Disease
- Cerebrovascular Disease

Combination of Micro- and Macrovascular complications:

- Diabetic Foot
- Erectile Dysfunction

2

SLIDE 2

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.

3

SLIDE 3

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.

4

SLIDE 4

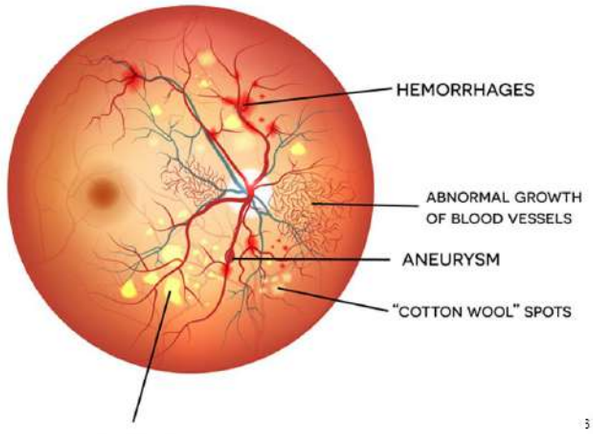
Eye Examination

- 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.

5

SLIDE 5

DIABETIC RETINOPATHY



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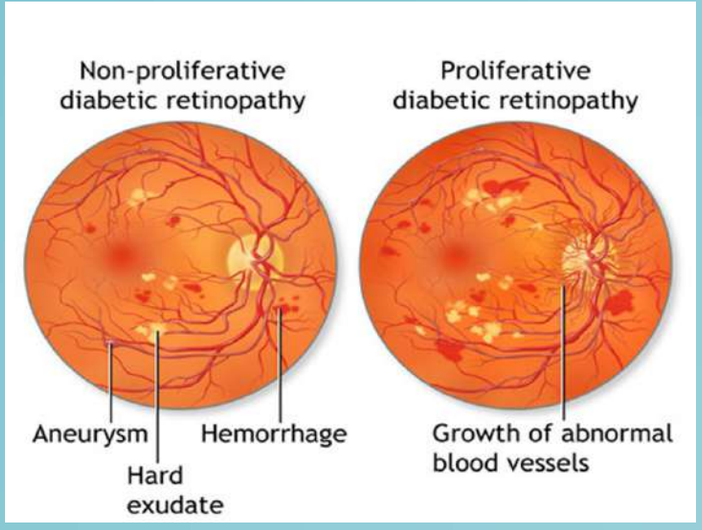
SLIDE 6



SLIDE 7

Referral to Ophthalmologist

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

8

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.

SLIDE 8

Urgent Referral to Ophthalmologist

Urgency of referral	Ocular features
Emergency (same day referral)	• Sudden severe visual loss • Symptoms or signs of acute retinal detachment
Appointment within 1 week	• Presence of retinal new vessels • Preretinal haemorrhage • Vitreous haemorrhage • Rubeosis iridis
Appointment within 4 weeks	• Unexplained drop in visual acuity • Any form of maculopathy • Severe NPDR • Worsening retinopathy

*Adapted from Screening of Diabetic Retinopathy. Malaysia: Ministry of Health Malaysia and Academy of Medicine Malaysia;2011 [253 (Level III)]

9

SLIDE 9

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.

10

SLIDE 10

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).

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SLIDE 11

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]*

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SLIDE 12

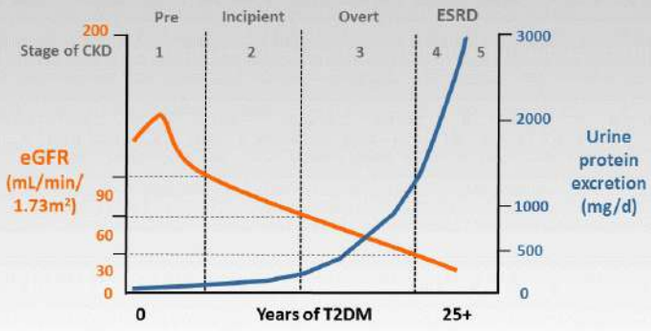
Nephropathy: Introduction

- Diabetic nephropathy is a major cause of chronic kidney disease (CKD) contributing to 58% of new patients requiring dialysis in 2012 in Malaysia. It is also major risk factor for cardiovascular morbidity and mortality.
- Diagnosis is made clinically by the presence of proteinuria. "Moderately increased albuminuria" and "severely increased albuminuria" are new term for microalbuminuria and overt proteinuria respectively.
- Progression to ESRD requiring renal replacement therapy occurs in majority of patients, particularly those with poor diabetic and blood pressure control.

13

SLIDE 13

Progression of CKD in T2DM



CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; T2DM = type 2 diabetes mellitus

Jerums G, et al. *Diabetes Res Clin Pract.* 2008;82(Suppl 1):S30-S37.
Williams ME. *Semin Dial.* 2010;23(2):129-133.
Slide courtesy of Clifford J. Bailey, PhD.

SLIDE 14

Nephropathy: Screening

- Standard urine dipstick test for proteinuria should be performed in all diabetic patients at diagnosis and annually.
- If the test is negative, it is recommended to screen for microalbuminuria using the first morning urine sample or random urine sample without excessive water intake.
- Microalbuminuria is the earliest sign of diabetic nephropathy and predicts increased cardiovascular mortality and morbidity and ESRD.
- If microalbuminuria is detected, a repeat test should be done within 3 to 6 months for confirmation. If it is negative, annual screening should be continued.

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

SLIDE 15

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.

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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.

SLIDE 16

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.

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SLIDE 17

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]*

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SLIDE 18

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.

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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.

SLIDE 19

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 contra-indicated to slow progression of diabetic nephropathy.
- Other measures:
  - Lipid control
  - Stop smoking
  - Weight reduction
  - Moderate protein and salt restriction

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SLIDE 20

Stages of CKD

Stage	Description	GFR (mL/min/1.73 m^2 body surface area)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End Stage Renal Disease	15 or dialysis

* Kidney damage defined as abnormalities on pathological, urine, blood, or imaging tests. *Adapted from National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease [276 (Level III)]

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SLIDE 21

Staging of Chronic Kidney Disease

GFR categories (mL/min/1.73 m^2) Description and range	Previous NKF CKD stage	Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category			Persistent albuminuria categories Description and range		
					A1	A2	A3
					Normal to mildly increased	Moderately increased	Severely increased
					<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	1	G1	Normal or high	≥90	1 if CKD	1	2
	2	G2	Mildly decreased	60-89	1 if CKD	1	2
	3	G3a	Mild to moderately decreased	45-59	1	2	3
		G3b	Moderately to severely decreased	30-44	2	3	3
	4	G4	Severely decreased	15-29	3	3	4+
	5	G5	Kidney failure	<15	4+	4+	4+

CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.
Levey AS, et al. *Kidney Int.* 2011;80:17-28.

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 g/mmol)
3. Haematuria
4. Rapidly declining renal function (loss of glomerular filtration rate/GFR >5 ml/min/1.73 m^2 in one year or >10 ml/min/1.73 m^2 within five years)
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

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

SLIDE 23

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]*

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SLIDE 24

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).

25

SLIDE 25

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%.

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SLIDE 26

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 biothensiometer
- The above increases the sensitivity of detecting peripheral neuropathy by 87%.
- These bedside tests should be performed at least annually.

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SLIDE 27

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.

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SLIDE 28

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.

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SLIDE 29

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 metoclopromide (maximum for 5 days) may be used in severe cases.

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SLIDE 30

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]*

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TOPIC

13

Case Study

management of chronic complications 1

SLIDE 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.

SLIDE 2

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.

SLIDE 3

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

SLIDE 4

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

SLIDE 5

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.

SLIDE 6

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)

SLIDE 7

Question:

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

SLIDE 8

Question

- Why need to have Diabetic eye Screening?

SLIDE 9

Why need to have Diabetic eye Screening?

Magnitude of disease	affect at least 50% Diabetic
Seriousness	Permanent visual impairment
Early detection	is possible- fundus assessment
Screening tests	available , cost effective, not too difficult and safe (ophthalmoscopy ,fundus camera)
Early treatment	available, acceptable and effective to preserve visual loss

SLIDE 10

Question?

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

SLIDE 11

CPG Schedule for Fundus Examination

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

•**Audit NDR 2012 – 44% diabetics had eye checked**

SLIDE 12

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

Lecture Notes

TOPIC

14

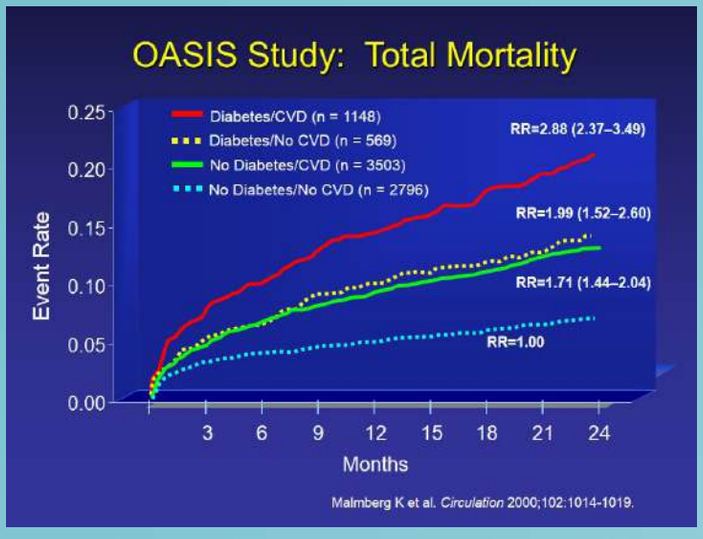
management of chronic complications 2

SLIDE 1

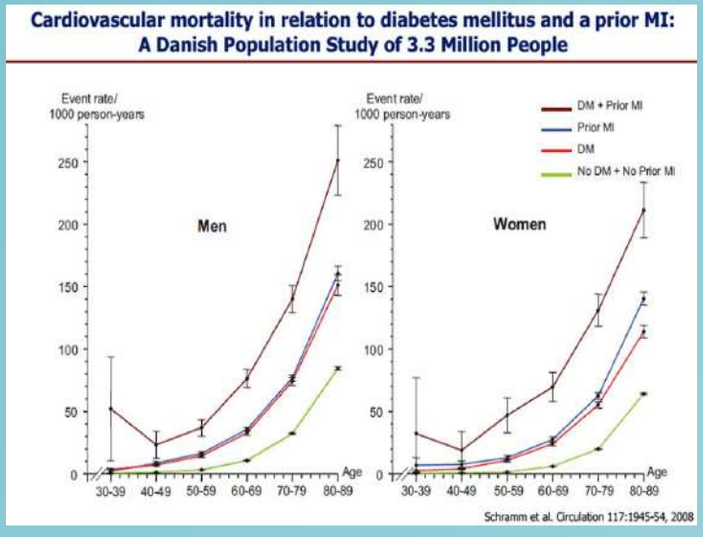
Coronary Heart Disease

- Diabetic patient 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 .

SLIDE 2



SLIDE 3

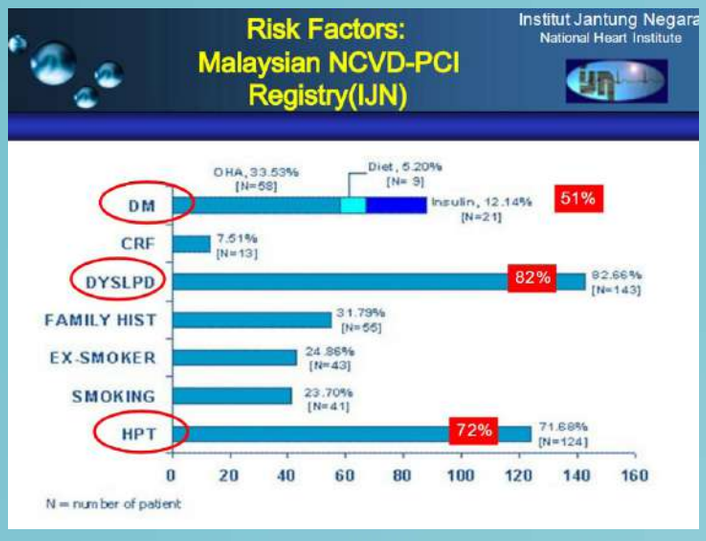


SLIDE 4

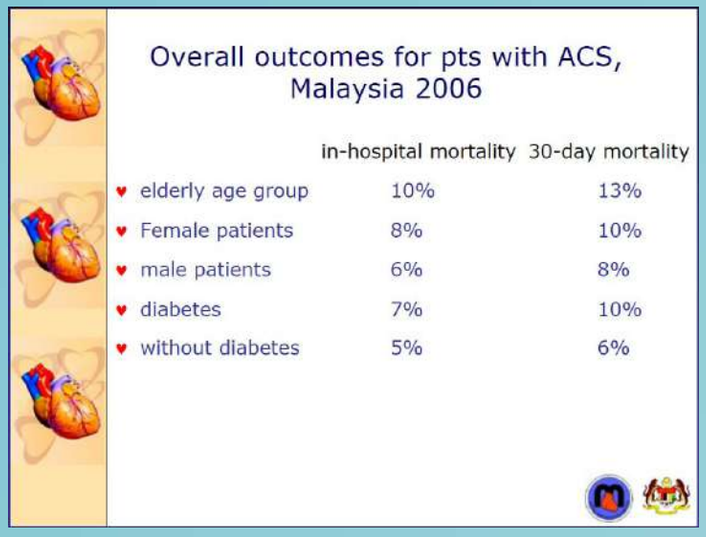
NCVD-ACS Registry

CV Risk factors	2006 (N=3392)	2007 (N=3640)	2008 (N=2839)	2009 (N=3594)	2010 (N=3401)	Total (N=16,866)
Dyslipidaemia	33	35	31	35	32	33
Hypertension	61	63	56	64	61	61
Diabetes	44	44	38	44	44	43
Family History of premature CVD	12	13	9	9	13	11
MI history	16	18	13	26	20	19
Documented CAD	15	18	14	20	16	17
New onset angina (<2 weeks)	45	53	48	68	60	55
Chronic angina (onset > 2 weeks ago)	15	11	8	12	10	11
Peripheral vascular disease	1	1	1	1	1	1
Cerebrovascular disease	4	3	3	3	4	4
Current Smoker	33	34	34	34	34	33
BMI > 23kgm^{-2}	75	74	73	76	75	75

SLIDE 5



SLIDE 6



SLIDE 7

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.

SLIDE 8

ASA and diabetes: 2008 JPAD

JAMA®

Online article and related content current as of November 9, 2008.

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial

Hisao Ogawa; Masafumi Nakayama; Takeshi Morimoto; et al.

JAMA. published online Nov 9, 2008; (doi:10.1001/jama.2008.623)

Clinical outcomes	HR (95% CI)	p
Primary end point*	0.80 (0.58–1.10)	0.16
Fatal coronary or cerebrovascular events	0.10 (0.01–0.79)	0.0037
All-cause mortality	0.90 (0.57–1.14)	0.67
Atherosclerotic events* (among age >65 y)	0.68 (0.46–0.99)	0.047

*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

SLIDE 9

ASA and diabetes: 2008 JPAD: Baseline clinical characteristics

Characteristic	Aspirin Group (n = 1262)	Nonaspirin Group (n = 1277)
Age (y)*	65 ± 10	64 ± 10
Male, n (%)	706 (56)	681 (53)
Current smoker, n (%)	289 (23)	248 (19)
Body mass index (kg/m²)*	24 ± 4	24 ± 4
Hypertension, n (%)	742 (59)	731 (57)
Dyslipidemia, n (%)	680 (54)	665 (52)
Duration of diabetes (y), median (IQR)	7.3 (2.8-12.3)	6.7 (3.0-12.5)
Systolic blood pressure (mm Hg)*	136 ± 15	134 ± 15
Diastolic blood pressure (mm Hg)*	77 ± 9	76 ± 9

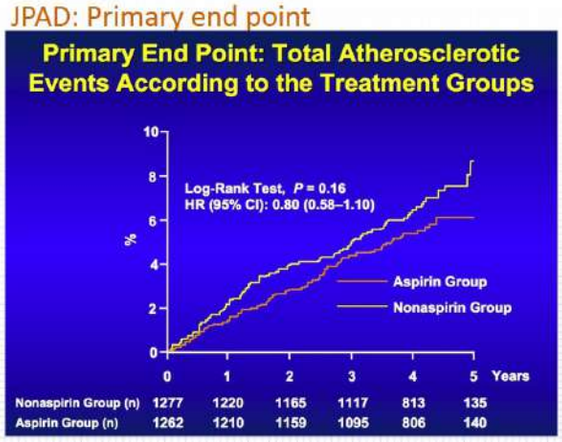
*Mean ± SD.

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

SLIDE 10

ASA and diabetes: 2008

JPAD: Primary end point

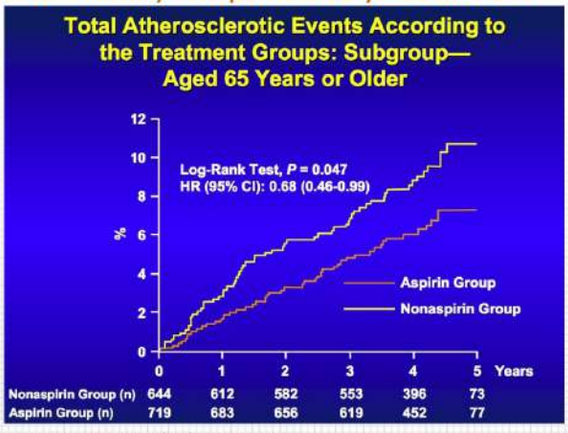


Ogawa H et al. JAMA 2008 (300) 18; 2134-2141

SLIDE 11

ASA and diabetes: 2008

JPAD: Primary end point if 65 years or older



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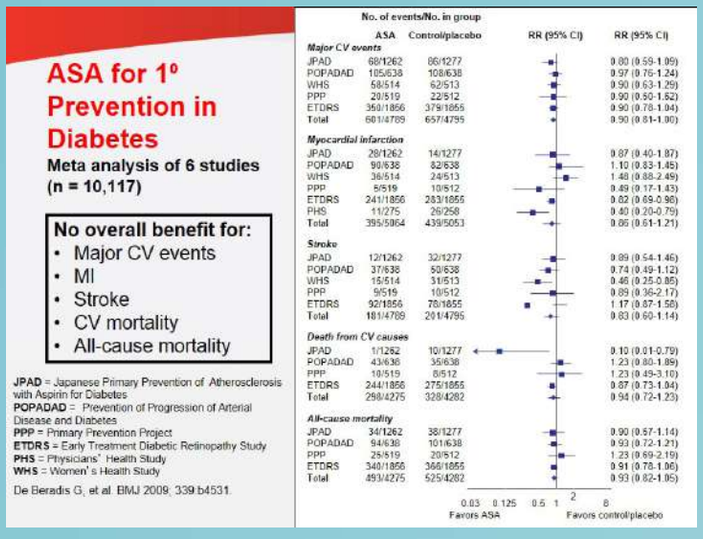
SLIDE 12



SLIDE 13

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.

SLIDE 14

Cerebrovascular Disease

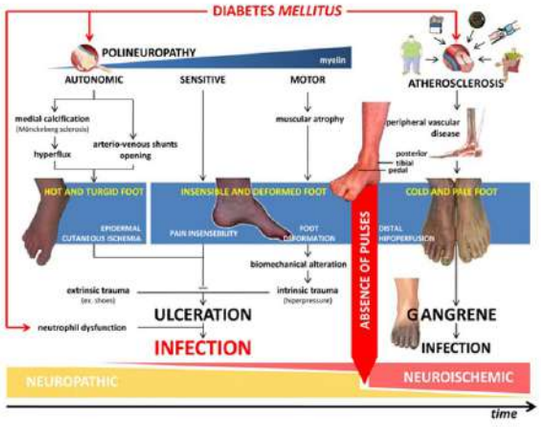
- Risk are increase twice of ischaemic stroke compared to those without diabetes.
- The risk of stroke is higher in women than in men.
- Dyslipidaemia, endothelial dysfunction and platelet or coagulation abnormalities are among the risk factors that promote the development of carotid atherosclerosis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

SLIDE 15

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

SLIDE 16



SLIDE 17

Prevention of Foot Ulcers

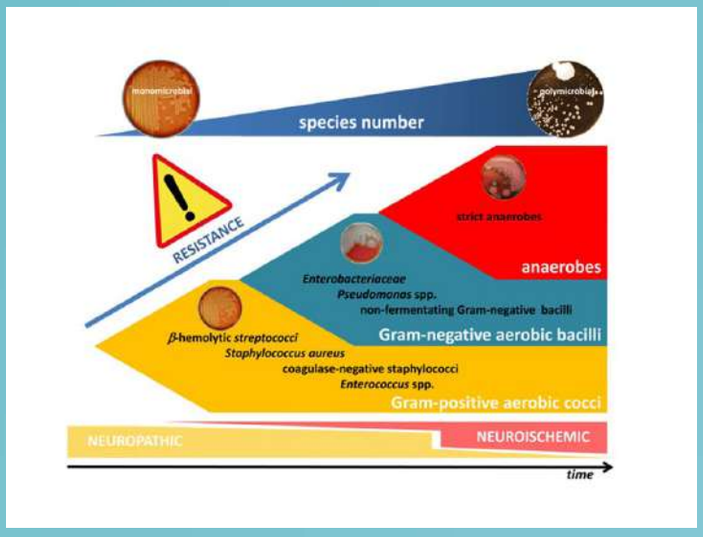
- Starts with examination of the feet (shoes and socks removed) and identifying those at high risk of ulceration. Assess the peripheral neuropathy and peripheral pulses.
- At-risk patients are then given relevant education to reduce the likelihood of future ulcers.
- The feet should be examined at least once annually or more often in the presence of risk factors.

SLIDE 18

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).

SLIDE 19



SLIDE 20

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

SLIDE 21

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

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

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

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

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, methyldopa 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.

SLIDE 25

Screening and Diagnosis

Figure 6: Sexual Symptom Checklist for Women

Sexual Symptom Checklist for Women

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function? Yes / No

If No, please continue.

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

- 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.fsfiquestionnaire.com. The validated Malay version is also available.

SLIDE 26

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.

SLIDE 27

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

TOPIC

14

Case Study

management of chronic complications 2

SLIDE 1

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. Atovarstatin 20 mg daily

Physical:
Wt 62 kg, BMI 23 kg/m^2, 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 & Atovarstatin 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

SLIDE 4

Basal insulin 24 units at bedtime
Gliclazide 60 mg daily
Metformin 850 mg BID

1. How would you have modified her diabetes treatment?
2. What will you do now?

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

SLIDE 5

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

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

MDI = Multiple daily injections, [$] Intensify involve changing the regimen; SU = sulphonylureas

Box 1: Selection of Anti-diabetic Agents

SU
Meglitinide
AGI
TZD
DPP-4i
GLP-1 RA
SGLT2i

Colour coded based on efficacy, risk of hypo & weight gain

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

SLIDE 6

Basal insulin 24 units at bedtime
Gliclazide 60 mg daily
Metformin 850 mg BID

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?

Lab results:

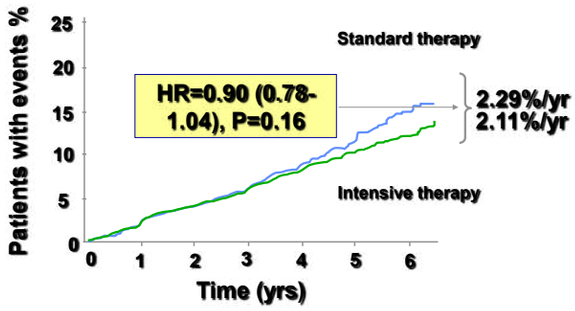
A1c 8.4 %
FBG 6.8 mmol/l

LDL 1.8 mmol/l
HDL 1.2 mmol/l
TG 1.8 mmol/l

Normal renal function
No proteinuria

SLIDE 7

ACCORD Treatment Effect on Primary Outcome

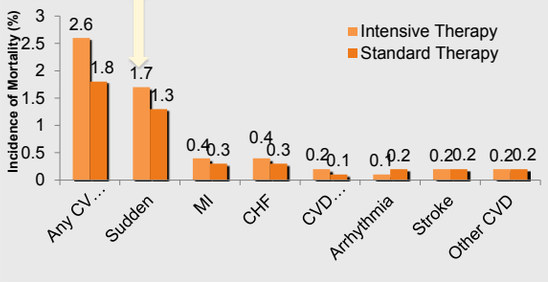


ACCORD Study Group *N Engl J Med* 358:2545-59; 2008

SLIDE 8

Cardiovascular Deaths in ACCORD

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

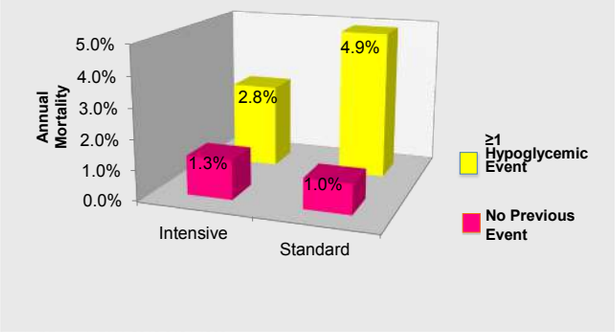


ACCORD. *N Engl J Med.* 2008;358:2545-2559.

SLIDE 9

Mortality Associated with Severe Hypoglycemia

ACCORD

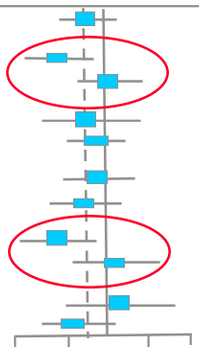


Bonds DE, et al. *BMJ.* 2010;340:b4909.

SLIDE 10

ACCORD: Hazard Ratios for Primary Outcome by Subgroup

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



ACCORD Study Group *N Engl J Med* 358:2545-59;2008.

SLIDE 11

Background: Mortality By Severe Hypoglycemia

	Never Experienced a Hypoglycemic Event	Experienced Hypoglycemic Event
Overall Mortality Rates	1.2% / year	3.3% / year
Intensive Glycemia	1.3% / year	2.8% / year
Standard Glycemia	1.1% / year	4.9% / year

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

SLIDE 12

Mortality By Treatment Group and Severe Hypoglycemia

	Overall	Never Experienced a Hypoglycemic Event	Experienced Hypoglycemic Event
Intensive Glycemia	1.4% / year (257 Deaths)	1.3% / year (223 Deaths)	2.8% / year (34 Deaths)
Standard Glycemia	1.1% / year (203 Deaths)	1.1% / year (186 Deaths)	4.9% / year (17 Deaths)
Hazard Ratio (95% CI)	1.22 (1.01, 1.46)	1.24 (1.02, 1.50)	0.54 (030, 0.96)
		Mortality Higher in Intensive Group	Mortality Higher in Standard Group

Interaction P < 0.01

SLIDE 13

Basal insulin 24 units at bedtime
Gliclazide 60 mg daily
Metformin 850 mg BID

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 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

SLIDE 14

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. Hyperlipdaemia 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

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

SLIDE 15

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

1. What will you do next ?

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

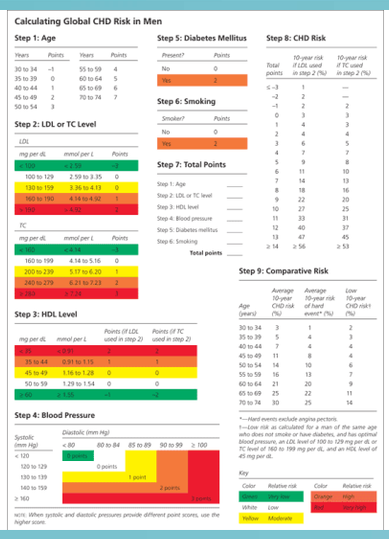
Lab results:

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

SLIDE 16



Calculating Global CHD Risk in Men

Step 1: Age

Years	Points	Years	Points
30 to 34	–1	55 to 59	4
35 to 39	0	60 to 64	5
40 to 44	1	65 to 69	6
45 to 49	2	70 to 74	7
50 to 54	3		

Step 2: LDL or TC Level

LDL

mg per dL	mmol per L	Points
< 100	< 2.59	–3
100 to 129	2.59 to 3.35	0
130 to 159	3.36 to 4.13	0
160 to 190	4.14 to 4.92	1
> 190	> 4.92	2

TC

mg per dL	mmol per L	Points
< 160	< 4.14	–3
160 to 199	4.14 to 5.16	0
200 to 239	5.17 to 6.20	1
240 to 279	6.21 to 7.23	2
≥ 280	≥ 7.24	3

Step 3: HDL Level

mg per dL	mmol per L	Points (if LDL used in step 2)	Points (if TC used in step 2)
≥ 60	≥ 1.55	–2	–2
50 to 59	1.29 to 1.54	0	0
40 to 49	1.03 to 1.28	1	1
35 to 44	0.91 to 1.15	2	2
< 35	< 0.91	5	5

Step 4: Blood Pressure

Systolic (mm Hg)	Diastolic (mm Hg) < 80	80 to 84	85 to 89	90 to 99	≥ 100
< 120	0 points				
120 to 129		0 points	1 point	2 points	3 points
130 to 139					
140 to 159					
≥ 160					

NOTE: When systolic and diastolic pressures provide different point scores, use the higher score.

Step 5: Diabetes Mellitus

Present?	Points
No	0
Yes	2

Step 6: Smoking

Smoker?	Points
No	0
Yes	2

Step 7: Total Points

Step 1: Age _____
Step 2: LDL or TC level _____
Step 3: HDL level _____
Step 4: Blood pressure _____
Step 5: Diabetes mellitus _____
Step 6: Smoking _____
Total points _____

Step 8: CHD Risk

Total points	10-year risk if LDL used in step 2 (%)	10-year risk if TC used in step 2 (%)
≤ –3	1	—
–2	2	—
–1	2	2
0	3	3
1	4	3
2	4	4
3	6	5
4	7	7
5	9	8
6	11	10
7	14	13
8	18	16
9	22	20
10	27	25
11	33	31
12	40	37
13	47	45
≥ 14	≥ 56	≥ 53

Step 9: Comparative Risk

Age (years)	Average 10-year CHD risk (%)	Average 10-year risk of hard event* (%)	Low 10-year CHD risk† (%)
30 to 34	3	1	2
35 to 39	5	4	3
40 to 44	7	4	4
45 to 49	11	8	4
50 to 54	14	10	6
55 to 59	16	13	7
60 to 64	21	20	9
65 to 69	25	22	11
70 to 74	30	25	14

*—Hard events exclude angina pectoris.
†—Low risk as calculated for a man of the same age who does not smoke or have diabetes, and has optimal blood pressure, an LDL level of 100 to 129 mg per dL or TC level of 160 to 199 mg per dL, and an HDL level of 45 mg per dL.

Key

Color	Relative risk	Color	Relative risk
Green	Low	Orange	High
White	Low	Red	Very high
Yellow	Moderate		

Patient's Score

Age = +3
LDL = -3
HDL = +2
BP = +1
DM = +2
Smoke= +2

Total= 7

14% 10-year Risk

SLIDE 17

He ask 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

SLIDE 18

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

Glycaemic Control / Current Treatment	A1c 6.5–< 7.5% or FPG 6–<8 mmol/L	A1c 7.5–<8.5% or FPG 8–<10 mmol/L	A1c 8.5–10.0% or FPG 10–13 mmol/L	A1c >10.0% or FPG >13 mmol/L
Lifestyle Treatment	Start metformin (if metformin not tolerated, use an agent from **Box 1**)	Start metformin and another agent from **Box 1** (dual therapy)	Start metformin and 2 other agents from **Box 1** (triple therapy)	Start metformin & another agent + insulin (basal or premixed od)
Monotherapy (Metformin preferred)	Add 1 agent from **Box 1** (dual therapy)	Add 2 agents from **Box 1** (triple therapy)	Add 2 agents from **Box 1** + insulin (basal or premixed od)	Initiate & intensify[3] insulin (MDI) and continue metformin
Dual Therapy	Add 1 agent from **Box 1** (triple therapy)	Add 1 agent from **Box 1** or insulin (basal or premixed od)	Add 1 agent from **Box 1** + insulin (basal or premixed od)	Initiate & intensify[3] insulin (MDI) and continue dual therapy (except SU/glinides)
Triple Therapy	Add 1 agent from **Box 1** (quadruple therapy)	Add 1 agent from **Box 1** or insulin (basal or premixed od)	Add insulin (basal or premixed od) and continue triple therapy[1]	Initiate & intensify[3] insulin (MDI) and continue triple therapy (except SU/glinides)

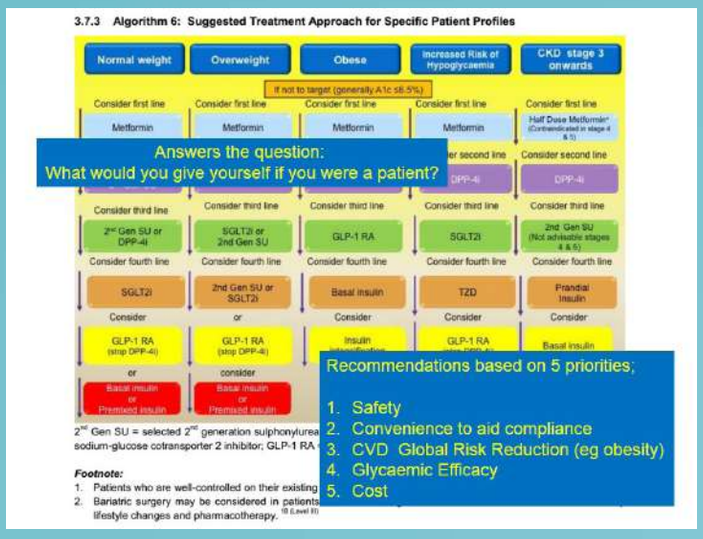
MDI = Multiple daily injections; [3] Intensify involve changing the regimen; SU = sulphonylureas

Box 1: Selection of Anti-diabetic Agents

SU
Meglitinide
AGI
TZD
DPP-4i
GLP-1 RA
SGLT2i

Colour coded based on efficacy, risk of hypo & weight gain

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


3.7.3 Algorithm 6: Suggested Treatment Approach for Specific Patient Profiles
Normal weight
Overweight
Obese
Increased Risk of Hypoglycaemia
CKD stage 3 onwards
If not to target (generally A1c ≤6.5%)
Consider first line
Metformin
Half Dose Metformin*
Consider second line
DPP-4i
Consider third line
2nd Gen SU or DPP-4i
SGLT2i or 2nd Gen SU
GLP-1 RA
SGLT2i
2nd Gen SU
Consider fourth line
SGLT2i
2nd Gen SU or SGLT2i
Basal insulin
TZD
Prandial Insulin
Consider
GLP-1 RA
Insulin
Basal insulin
or
consider
Basal insulin or Premixed insulin
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. CVD Global Risk Reduction (eg obesity)
4. Glycaemic Efficacy
5. Cost
Footnote:
1. Patients who are well-controlled on their existing
2. Bariatric surgery may be considered in patients
lifestyle changes and pharmacotherapy.

TOPIC

15

Lecture Notes

diabetes in special populations 1

SLIDE 1

Diabetes in Pregnancy

- Gestational diabetes mellitus
- Pre existing Type1 and Type2 DM

SLIDE 2

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

SLIDE 3

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

SLIDE 4

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.

SLIDE 5

GDM- risk in the subsequent pregnancies

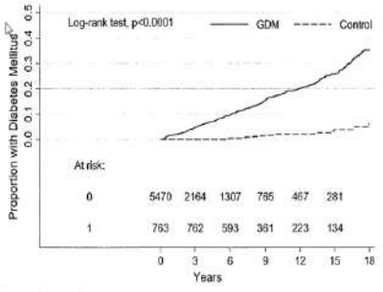
Race/ethnicity*	GDM criteria†	GDM (n)	Age at index pregnancy (years)	Time between pregnancies‡	Rate of GDM recurrence (%)
NHW					
NHW (Dutch)	Center specific	58	27§	12–48 months	30
NHW (Nova Scotia)	1979 NDDG	651	?	?	33
93% NHW (Australia)	ADIPS	100	28	2.4 years	35
NHW (?) (Australia)	Center specific	865	29	?	37
NHW (?) (Australia)	1979 NDDG	19	?	<12 months	84
NHW and minority					
64% NHW, 36% nonwhite (Cleveland)	1979 NDDG	36	28	?	56
80% NHW, 20% non–English speaking, country of birth, including Mediterranean countries (Australia)	ADIPS	117	27	<6 years	62
84% NHW (Washington)	Birth certificate	1,322	?	?	OR 23
Predominantly minority, including Latinas					
81% African American	1979 NDDG	90	24	?	52
93% Latina	1979 NDDG	164	28	<48 months	68
85% Latina	1979 NDDG	78	30	<48 months	69
Japanese	JDS	32	27	26–33 months	66
Asian (Chinese, Filipina, Sri Lankan, Vietnamese)	Center specific	258	?	?	OR 15

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

SLIDE 6

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.

SLIDE 7

GDM

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

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.

SLIDE 8

Diagnostic criteria -GDM

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

* Adapted from the American Diabetes Association–Standards of Medical Care in Diabetes–2015,4 (Level III) The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management and care,422 (Level III) International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations on the diagnosis and classification of hyperglycemia in pregnancy,423 (level III) and World Health Organization (WHO): Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy, 424 (Level III)
** Adapted from NICE Guidance on Diabetes in Pregnancy: Management of Diabetes and its Complications from Preconception to the Postnatal Period, 2015, 421 (Level III) These levels are adopted in view of the fact that T2DM is diagnosed in Asians at lower A1c, body mass index and waist circumference levels compared to the West.

SLIDE 9

When to screen

- Universal screening should be performed between week 24 to 28 if there is enough resources.
- Otherwise ,screen the individuals at high risk of developing GDM at booking.
- If the those with high risks have normal result , then a repeat OGTT should be done 4-6 weeks later

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.

SLIDE 10

Screening - risk factors

- BMI >27 kg/m^2
- 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)

SLIDE 11

Method of screening

- 75-g OGTT
  0' and 120' plasma glucose measurements
- Fasting plasma glucose (FPG)

SLIDE 12

Pregnancy and Pre-existing diabetes

- Preconception counselling
- Provided by a multidisciplinary team, which includes physician, obstetrician, dietitian, diabetes nurse educator and other health care providers.

SLIDE 13

Pre-conception Counselling

- Pregnancy has to be planned.
- The importance of smoking cessation.
- The time, commitment and effort required by the patient in both self-management and engagement with the health care team.
- The importance of notifying the health care team without delay in the event of conception.

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.

SLIDE 14

Pre-conception Management

- Keep the A1c as normal as possible (<6.5%).
- Weight reduction in those overweight and obese.
- Folic acid supplementation started 3 months before withdrawal of contraception.

SLIDE 15

Pre-conception Management

- OAD(s) can be switched to insulin for better glycaemic control
- Insulin treated women should be on multiple daily doses (basal-bolus) of insulin.
  - Multiple daily doses of short-acting human insulin have been used safely and effectively.
  - Rapid acting insulin analogues may be used to achieve better 1-hour postprandial glycaemic.
  - Control with less hypoglycaemia although perinatal outcomes are similar to human insulin.
  - Insulin detemir has similar efficacy as NPH insulin but with less nocturnal hypoglycaemia.
  - Insulin glargine has no RCT data but observational data suggest no adverse effects on 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.

SLIDE 16

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.

SLIDE 17

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

SLIDE 18

Glycaemic targets in pregnancy

Timing	Glucose Level (mmol/L)
Fasting or premeal	**≤ 5.3**
1 hour post prandial	**≤ 7.8**
2 hour post prandial	**≤ 6.7**

SLIDE 19

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.

SLIDE 20

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

SLIDE 21

Allowed Weight Gain

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

SLIDE 22

Insulin therapy

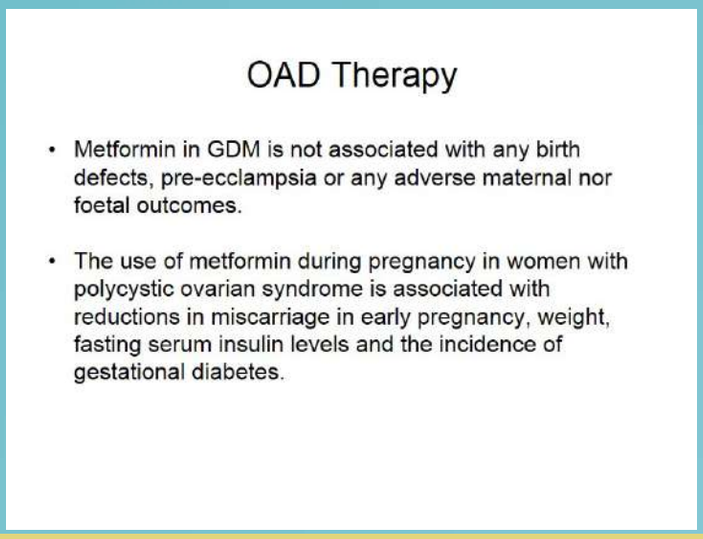
- Insulin therapy should be considered if the blood glucose targets are not met 1-2 weeks after introducing changes to diet and initiating exercise.
- Multiple daily injections is preferred for better glycaemic control.
- Use of short acting and long acting analogues – reduces the risk of hypoglycaemia.
- Short acting analogue will be able to control the post prandial hyperglycaemia.

SLIDE 23

Initiating Insulin

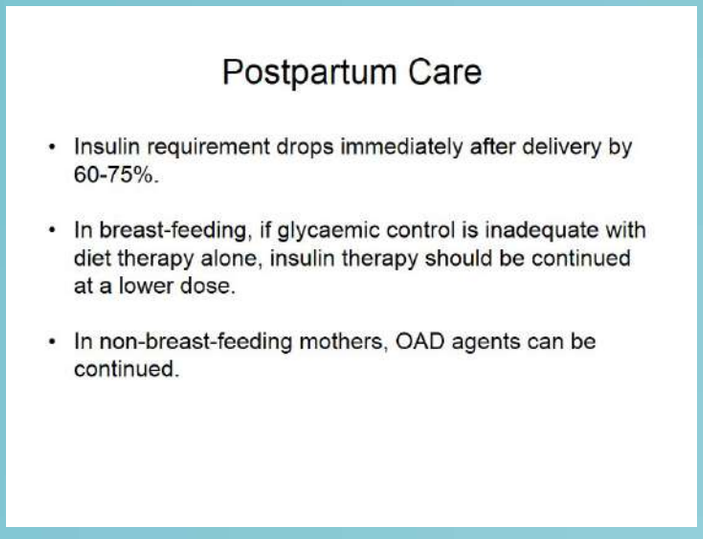
Glycaemic Abnormality	Suggested Insulin Type and Dose
FPG >5.1 mmol/L	• Start 0.2 units/kg of intermediate-acting insulin at bedtime, increase by 2 units every 3 days until targets are reached.
1-hour postprandial >7.8 mmol/L 2-hour postprandial >6.7 mmol/L	• Start 6 units of short-acting insulin, increase by 2 units every 3 days until targets are reached. • If pre-prandial short-acting insulin dose exceeds 16 units TDS, consider adding 6-10 units intermediate-acting insulin in the morning and titrate accordingly until targets are achieved.

SLIDE 24



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.

SLIDE 25



SLIDE 26

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.

SLIDE 27

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 done with a repeat OGTT in women with GDM.

TOPIC

15

Case Study

diabetes in special populations 1

SLIDE 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

SLIDE 2

Case 1

- BP – 130/80 mmHg
- BMI – 25 kg/m^2
- FBS – 7 mmol/L
- A1c – 7.5%

Patient is obese with suboptimal diabetes control.

SLIDE 3

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)

SLIDE 4

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

    or
  - Switch to basal-bolus insulin regime and stop the OAD

SLIDE 5

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/m^2.

SLIDE 6

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 has 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.

SLIDE 10

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.

SLIDE 11

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.

SLIDE 12

On Follow-up…

A month later her blood sugar started to increase

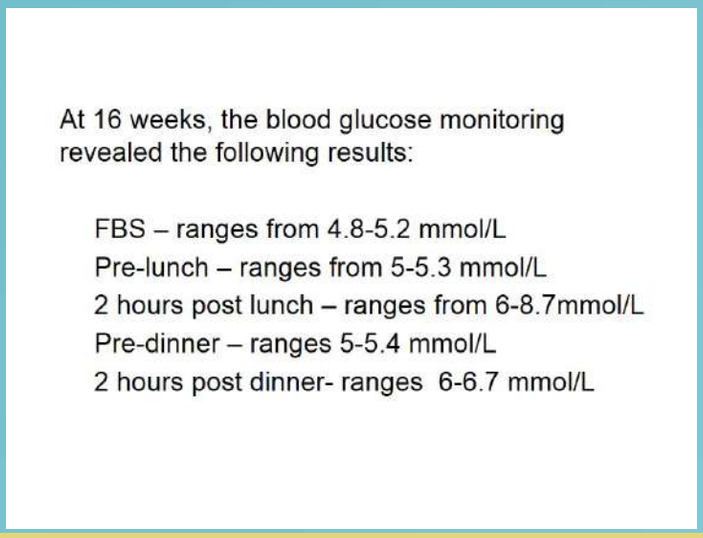
FBS – ranges from 4.8-5.2 mmol/L
Pre-lunch – ranges from 5-5.8 mmol/L
2 hours post lunch – ranges from 6-7.2mmol/L
Pre-dinner – ranges 5-6.0 mmol/L
2 hours post dinner- ranges 6-6.9 mmol/L

She was initiated on insulatard 10 u in the morning.

How do you monitor this patient?

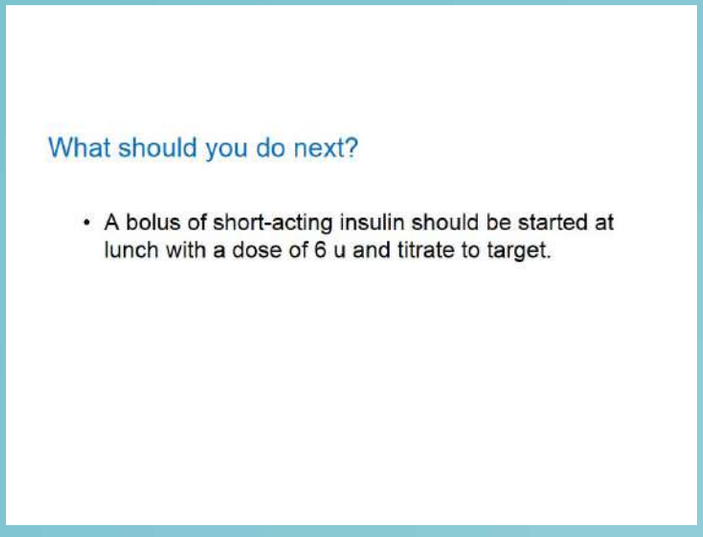
- The patient should monitor the blood glucose regularly.
- The fasting and pre-meals and postprandial blood glucose monitoring should be done.

SLIDE 13



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.

SLIDE 14



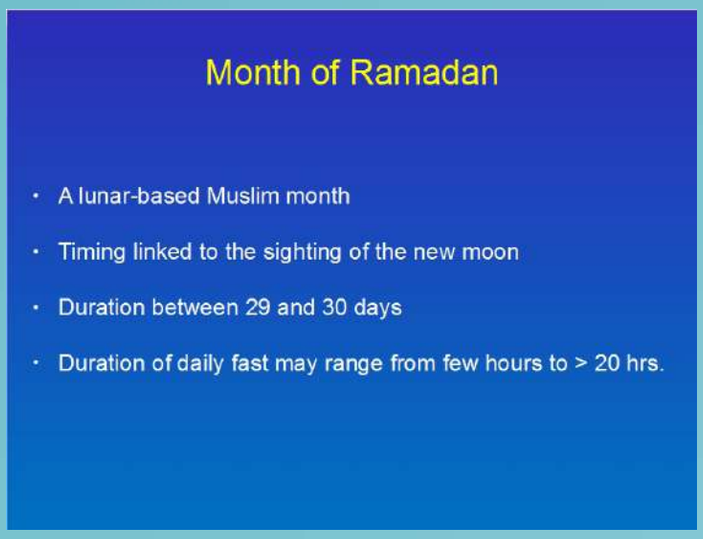
TOPIC

16

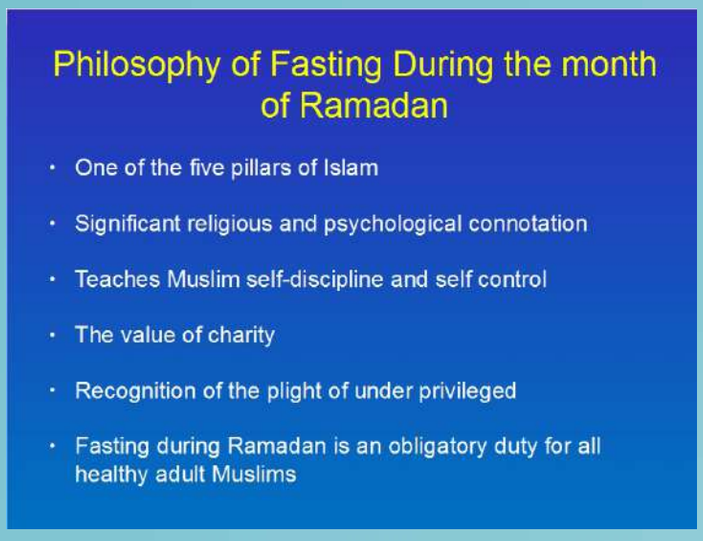
Lecture Notes

diabetes in special populations 2

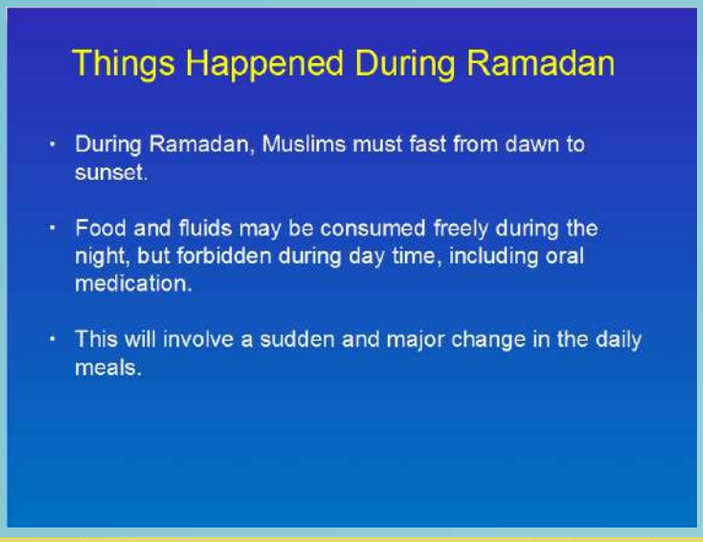
SLIDE 1



SLIDE 2



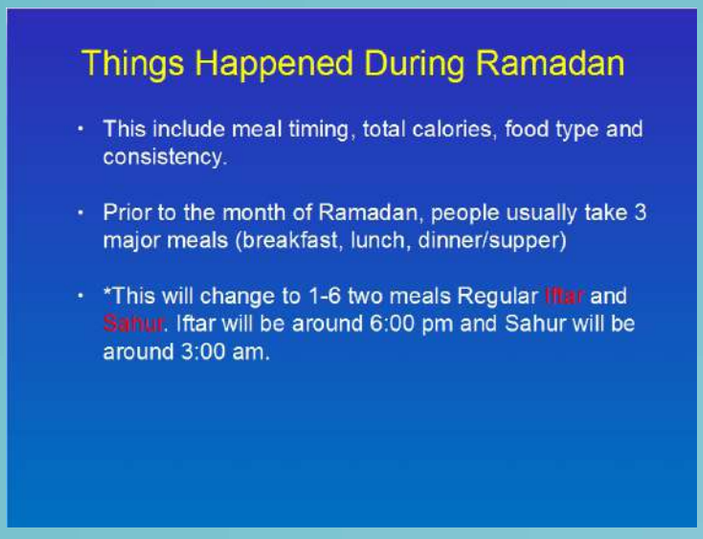
SLIDE 3



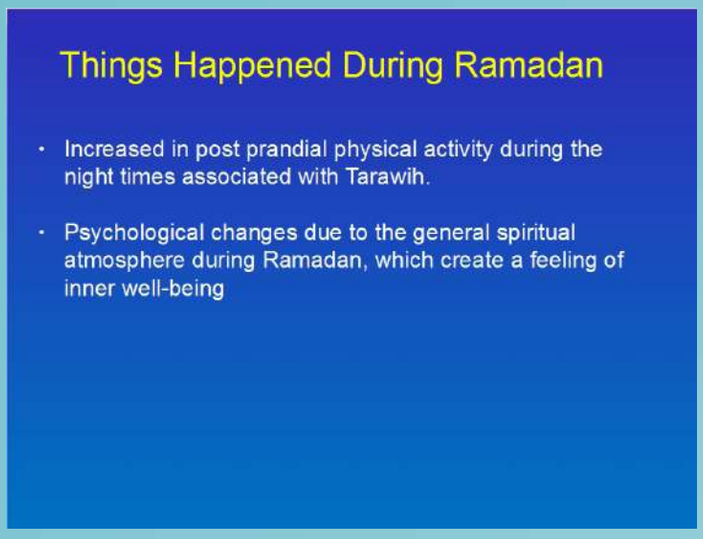
During Ramadan, eating habits change in many ways, not only do mealtimes change, but patterns of meals. There is an increase in post prandial physical activity during the night times associated with observation of religious practices (Tarawih). Psychological changes due to the

general spiritual atmosphere during Ramadan, which create a feeling of inner well-being, are also important.

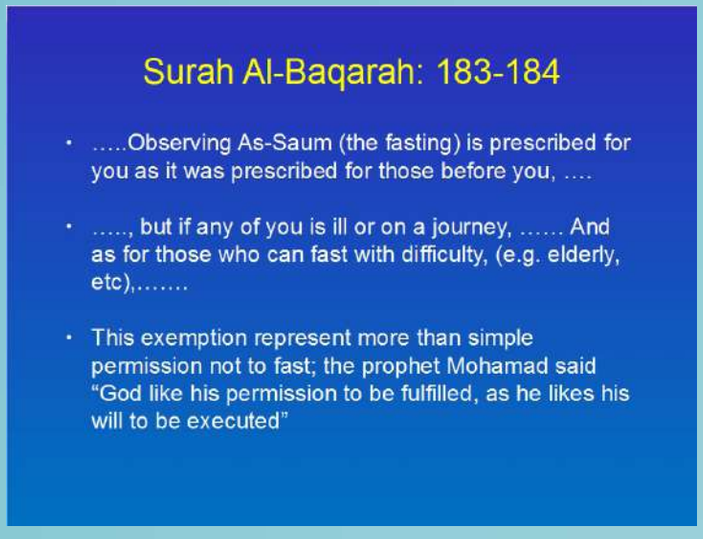
SLIDE 4



SLIDE 5



SLIDE 6



SLIDE 7

Major Risks associated With Fasting in Patients With Diabetes

- Hypoglycemia
- Hyperglycemia
- DKA
- Dehydration and thrombosis

SLIDE 8

Self-reported Hypoglycaemia Before and During Ramadan

Frequency of episodes per month

	Overall population			
	type 1 DM		type 2 DM	
	Before Ramadan	During Ramadan	Before Ramadan	During Ramadan
Non severe hypoglycaemia				
Mean (SD)	2.6 (4.9)	1.7 (3.0)	0.6 (1.7)	0.6 (1.9)
p	SS ($p < 0.001$)		NS ($p = 0.29$)	
Severe hypoglycaemia*				
Mean (SD)	0.03 (0.1)	0.14 (0.6)	0.004 (0.02)	0.03 (0.28)
p	SS ($p = 0.0174$)		SS ($p < 0.0001$)	

* : requiring hospitalisation

4.7X 7.5X

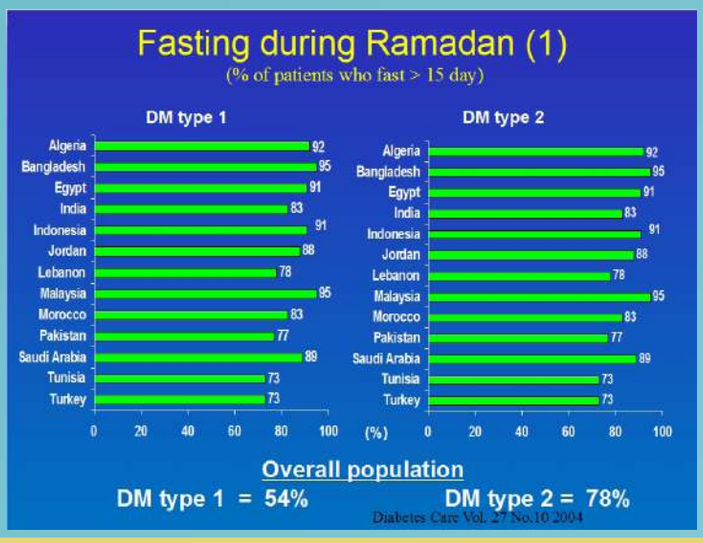
SLIDE 9

Severe hyperglycaemia before and during Ramadan

Frequency of episodes requiring hospitalisation per month

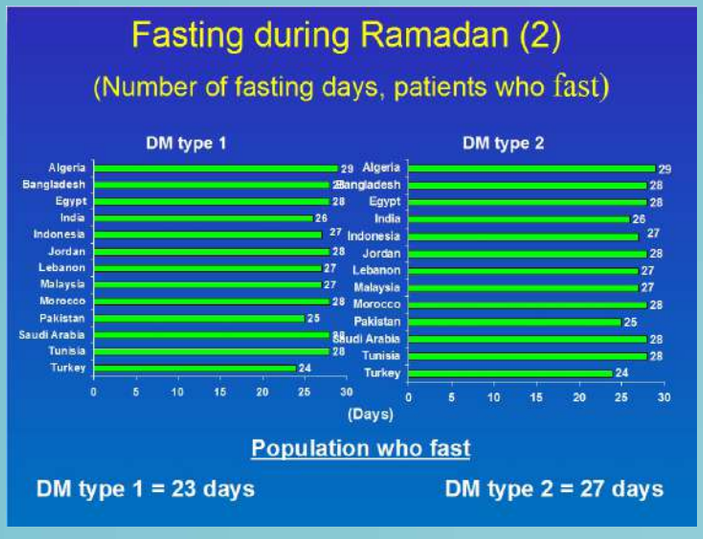
	DM-type 1		DM-type 2	
	Before Ramadan	During Ramadan	Before Ramadan	During Ramadan
Overall population				
	0.05	0.16	0.01	0.05
p	NS ($p = 0.16$)		SS ($p < 0.001$)	
Population who fasts				
Mean	0.05	0.20	0.009	0.04
p	SS ($p = 0.001$)		SS ($p < 0.0001$)	
	3X		5X	

SLIDE 10



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.

SLIDE 11



SLIDE 12

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

SLIDE 13

Categories of risks in patients with type 2 diabetes who fast during Ramadan

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

SLIDE 14

Categories of risks in patients with type 2 diabetes who fast during Ramadan

Moderate risk

- Well control patient treated with meglitinide

Low risk

- Diet alone, metformin/ TZD/DPP4-i/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

SLIDE 18

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

SLIDE 19

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

SLIDE 20

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)

SLIDE 21

Management

General Consideration

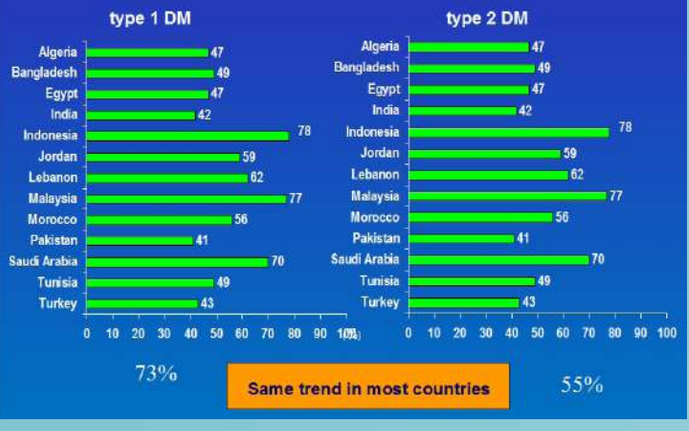
Breaking Fast

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



73%

Same trend in most countries

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

SLIDE 24

Management of T2DM

T2DM with Metformin

- May safely fast
- 2/3 total daily dose immediately before sunset meal
- 1/3 before pre-dawn meal

SLIDE 25

Management of T2DM

T2DM with TZD/DPP-4i /GLP-1 RA/SGLT2i/AGI

- No dose change required
- Low risk of hypoglycemia

SLIDE 26

Management of T2DM

T2DM with SU

- Newer SU is effective with less hypoglycaemia
- Avoid glibenclamide
- Chlorpropamide is absolutely contraindicated

SLIDE 27

Insulin Adjustments During Ramadan

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

SLIDE 28

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]*

TOPIC

16

Case Study

diabetes in special populations 2

SLIDE 1

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
- Diamicron MR 90 mg daily
- Amlodipine 10 mg daily
- Lovastatin 40 mg daily

SLIDE 2

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
- UFEME : protein ++
- SMBG:
  - FBS : 4-6.2mmol/L
  - Post-meal : >10 mmol/L

SLIDE 3

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?

CURRENT TREATMENT	FASTING
MIXTARD 30/20 UNIT BD	1. Reverse doses: morning dose at iftar & evening dose at sahur 2. Reduce dose at sahur by 20-50% to prevent daytime hypoglycaemia
METFORMIN 1 g BD	Take 1 g at iftar and sahur

SLIDE 8

When to do SMBG?

Therapy	Timing and frequency SMBG
Oral anti-diabetic (OAD)	Monitor when symptomatic[1]
Insulin	Diabetic patients who are in the moderate to high risk categories are advised to monitor their blood glucose 5 times per day[2] • Pre-meal and 2-hour post pre-dawn meal (*sahur*) • Mid-day • Pre-meal and 2-hour post sunset meal (*iftar*) • Bedtime

SLIDE 9

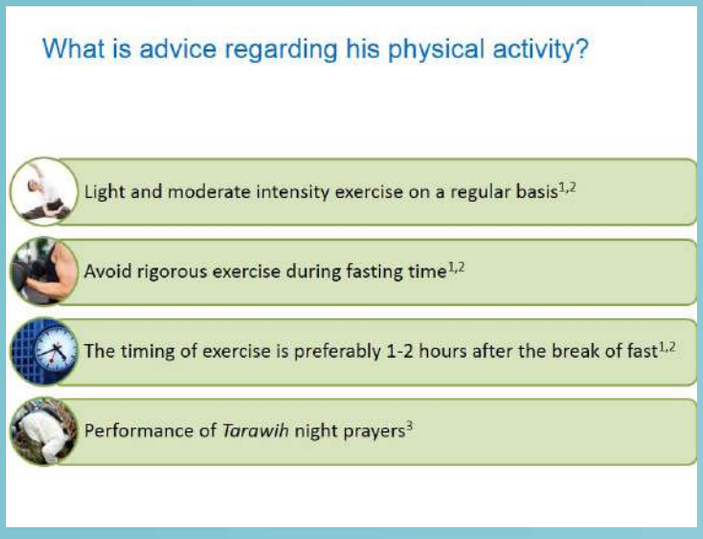
When to end fast?

Conditions to stop fasting:

- Blood glucose <3.3 mmol/l at anytime during the fast[1]
- Blood glucose <3.9 mmol/l in the first few hours of fasting (especially if the patient is taking sulfonylureas, meglitinides, or insulin)[2,3]
- Blood glucose >16.7 mmol/l[1]
- Experience symptoms of hypoglycaemia (patients without SMBG)[4]
- Symptoms suggestive of severe dehydration such as syncope and confusion[4]

SLIDE 10

SLIDE 11



TOPIC

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Lecture Notes

diabetes in special populations 3

SLIDE 1

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 versus1.5 to 2.0/100,000 person-years for T1DM.
- Common in adolescents coinciding with physiologic pubertal insulin resistance.

SLIDE 2

International Journal of
Environmental Research and
Public Health
ISSN 1660-4601
www.mdpi.com/journal/ijerph

Article

Lifestyle Practices and Obesity in Malaysian Adolescents

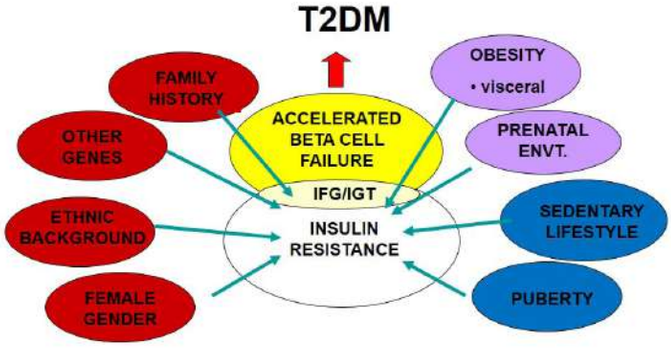
Pey Sze Teo [1,4], Abdullah Nurul-Fadhilah [1], Mohd Ezane Aziz [2], Andrew P. Hills [3] and Leng Huat Foo [1,*]

Table 1. General characteristics and body composition profiles (mean ± SD) of adolescent boys and girls by ethnicity, $n = 454$.

	Malay ($N = 236$)		Chinese ($N = 218$)	
	Boys ($N = 104$)	Girls ($N = 132$)	Boys ($N = 100$)	Girls($N = 118$)
Age, years	15.4 ± 1.9	15.2 ± 1.9	15.2 ± 1.9	15.4 ± 1.9
Body weight, kg	52.5 ± 14.1	48.5 ± 13.4 *	55.9 ± 15.0	51.2 ± 10.2 **
Height, m	1.6 ± 0.1	1.5 ± 0.1 ***	1.6 ± 0.1	1.6 ± 0.1 ***
BMI, kg/m^2	20.4 ± 4.3	20.6 ± 4.8	20.7 ± 4.2	21.1 ± 3.8
Thinness [a]	9.6 (10)	10.6 (14)	6.0 (6)	5.1 (6)
Normal	70.2 (73)	72.0 (95)	75.0 (75)	72.9 (86)
Overweight and obese	20.2 (21)	17.4 (23)	19.0 (19)	22.0 (26)
BMI z-score	0.03 ± 1.36	−0.10 ± 1.44	0.20 ± 1.32	0.15 ± 1.24
Pubertal status [a]				
Pre-pubertal	5.8 (6)	0.8 (1)	13.0 (13)	0.0 (0)
Pubertal	78.8 (82)	67.4 (89)	71.0 (71)	78.8 (93)
Post-pubertal	15.4 (16)	31.8 (42)	16.0 (16)	21.2 (25)
Dietary energy intake [b,c], kcal/day	2,408 (2,255–2,437)	2,178 ** (2,058–2,246)	1,860 (1,792–1,970)	1,649 * (1,642–1,828)

SLIDE 3

Primary Factors Contributing to Development of T2DM in Children



SLIDE 4

Atherosclerosis begins in Childhood

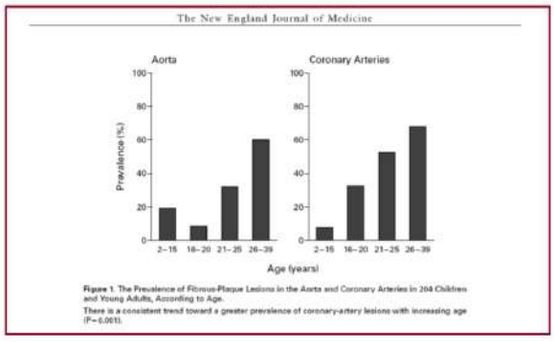
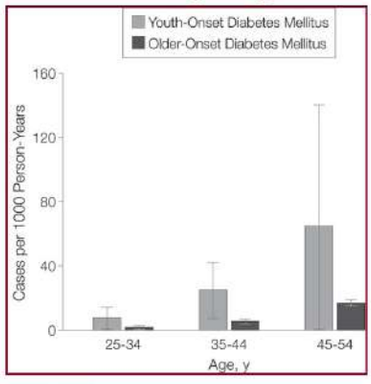


Figure 1. The Prevalence of Fibrous-Plaque Lesions in the Aorta and Coronary Arteries in 204 Children and Young Adults, According to Age.
There is a consistent trend toward a greater prevalence of coronary-artery lesions with increasing age ($P=0.001$).

Berenson GS, et.al. N Engl J Med, 1998

SLIDE 5

T2DM in childhood predisposes for earlier onset of nephropathic disease



Pavkov ME, et.al. JAMA, 2006

SLIDE 6

A National Database on Children and Adolescent with Diabetes (e-DiCARE): Results from April 2006 to June 2007

Table I: Number and Proportion of Basis of Diagnosis by Type of Diabetes Mellitus amongst those with known Basis Diagnosis, DiCARE April 2006-June 2007

Basis of Diagnosis		T1DM N=162		T2DM N=41	
		N	%	N	%
Incidental	Asymptomatic	2	1.2	1	2.4
Clinical	Diabetic ketoacidosis (DKA)	89	57.1	2	5.6
	Obesity	3	1.9	20	55.6
	Acanthosis nigricans	3	1.9	16	44.4
	Pruritis (genitalia)	2	1.3	5	13.9
	Recurrent abscess	1	0.6	0	0
	Weight loss	78	50.0	8	22.2
	Hyperosmolar symptoms (polyuria or polydipsia or secondary enuresis)	98	62.8	23	63.9
	Incomplete data	98		1	2.9
Biochemistry	RBS > 11.1 mmol/L (RBS)	122	89.1	23	69.7
	FBS > 7.0 mmol/L (FBS)	27	19.7	16	48.5
	OGTT (2 hours) > 11.1 mmol/L	3	2.2	8	24.2
	Insulin auto-antibodies	4	2.9	0	0
	C-peptide/ insulin level	17	12.4	5	15.2
	Ketonuria	94	68.6	4	12.1
	Ketoaemia (>0.5 mmol/L)	14	10.2	1	3
	$HCO3 < 15mmol/L$	54	39.4	1	3
	Incomplete data	0	0	1	3

Table II: Number, Mean and Median of HbA1c by Type of Diabetes Mellitus amongst those with known HbA1c study, DiCARE April 2006- June 2007

Type	N	Mean (SD)	Median (min, max)
T1DM	50	9.9 (2.0)	9.5 (6.8, 17.0)
T2DM	20	9.7 (2.8)	9.8 (5.2, 13.4)
Others	7	10.8 (3.7)	10.2 (6.8, 16.3)

SLIDE 7

Table 2.4.4.2 Glycaemic control of T1DM patients in the past 12 months, DiCARE 2006-2008 (N=48)

Profiles	n (%)
HbA_{1C} (%)	
• ≤7.5	12 (25.0)
• 7.6 - ≤ 8.9	4 (8.3)
• 9.0 - ≤ 10.0	6 (12.5)
• >10.0	26 (54.2)
Missing	76

Table 2.4.4.1 Glycaemic control by age group of T1DM patients in the past 12 months, DiCARE 2006-2008 (N=48)

Profiles	n	HbA_{1C} Mean (SD)	HbA_{1C} Median (IQR 1st - 3rd)	HbA_{1C} Min, max
Overall	48	10.8 (3.5)	11.4 (IQR 7.5 - 13.5)	5.4, 19.7
Age group				
• < 5 years	3	7.2 (1.0)	6.6 (IQR 6.6 - 7.5)	6.6, 8.4
• 5 - < 10 years	10	10.7 (3.3)	11.5 (IQR 7.2 - 13.3)	5.4, 15.1
• 10 - < 15 years	22	11.1 (3.6)	10.8 (IQR 8.2 - 13.9)	6.3, 19.7
• 15 - < 20 years	13	11.3 (3.5)	12.1 (IQR 7.8 - 14.3)	5.8, 17.1

SLIDE 8

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

t

SLIDE 9

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

Copeland KC, Zeitler P, Geffner M, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab.* 2011;96(1):159–167

SLIDE 15

Treatment T2: The TODAY Trial

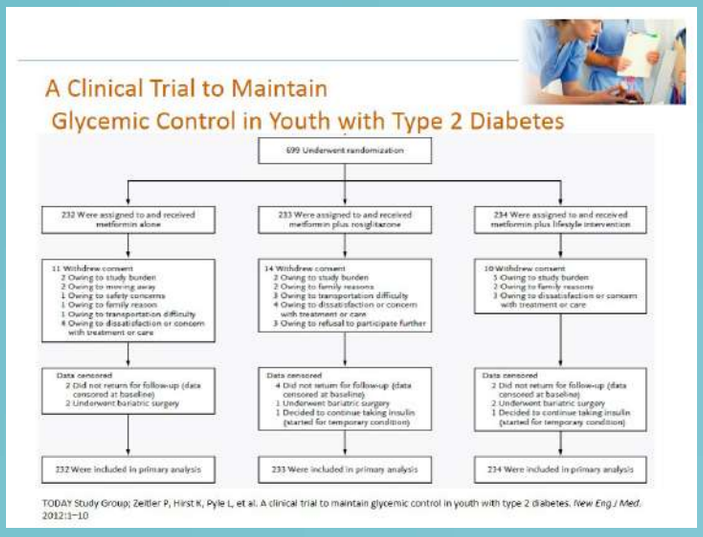
	Mean ± SD or %
Age (years)	14.3 ± 2.0
Race/Ethnicity	
White	19.6%
African American	37.4%
Hispanic	32.2%
Native American	5.5%
Other/Unknown	5.3%
BMI (kg/m²)	36.2 ± 7.9 25 - 71
BMI Z-score	+2.3 ± 0.5

Medications at Presentation

- No medication 11%
- Insulin only 12%
- Metformin only 49%
- Metformin + insulin 25%
- Other medication 4%

Copeland KC, Zeitler P, Geffner M, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab.* 2011;96(1):159–167

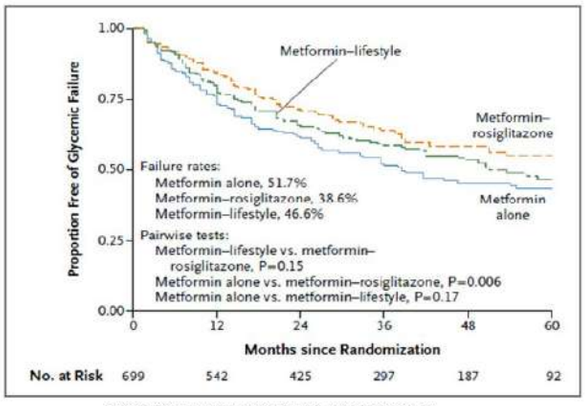
SLIDE 16



TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *New Eng J Med.* 2012:1–10

SLIDE 17

Treatment T2: The TODAY Trial Study Results



TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *New Eng J Med.* 2012:1–10

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.

SLIDE 19

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.

SLIDE 20

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

TOPIC

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Case Study

diabetes in special populations 3

SLIDE 1

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.

SLIDE 2

Examination/Investigations

- Lethargic looking
- Fungal infection over both groins
- BP 108/80 mmHg
- Weight : 86 kg; Height: 165 cm , BMI = 31.6 kg/m^2
- FBG = 16.1 mmol/L; A1c = 15.8%
- Urine ketone trace; urine protein negative
- Serum creatinine = 60 µmol/L

SLIDE 3

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

SLIDE 4

What is the diagnosis?

Type 2 diabetes mellitus

Reasons:

- No ketone
- Strong family history
- Obese
- Dyslipidaemia
- Chronicity / long-standing symptoms

SLIDE 5

How would you manage her?

Her treatment priority is controlling her blood glucose

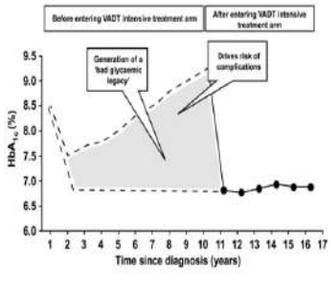
- Initiate insulin therapy (basal-bolus or bd premixed regimens) 0.5 u/kg/day

  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

SLIDE 6

Estimated glycaemic legacy of patients recruited in VADT[1]



[1] Del Prato S. Megatrials in type 2 diabetes. From excitement to frustration? Diabetologia. 2009;52(7):1219-26.

SLIDE 7

Treatment of other co-morbidities

- Dyslipidaemia
  - Start on statin
- Treat fungal infections in groins
  - Anti-fungal agent – miconazole cream

SLIDE 8

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%

SLIDE 9

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%

SLIDE 10

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

[1] Inzucchi S, Bergenstal R, Buse J, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: A Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2012;35(6):1364-1379.

SLIDE 11

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

SLIDE 12

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

SLIDE 13

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

SLIDE 14

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.

SLIDE 15

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[1]: 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

[1] Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366(24):2247-2256.

Lecture Notes

TOPIC

18

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 OGTT

Based on OGTT	Fasting (0 hr)	2 hr
IFG	6.1 – 6.9 mmol/L	-
IGT	-	7.8 – 11.0 mmol/L

2) Based on HbA_{1c}

	HbA_{1c}
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 NIDDM (Europe, Canada)

SLIDE 4

Scientific Evidence (cont.)

Study	Reduction in Risk (%)	
	Lifestyle	Drug
Da Qing[468]	31-46	-
DPS[467]	58	-
DPP[45]	58	31
Indian DPP[471]	28.5	26.4
Stop NIDDM[472]	-	25

45. Knowler WC, et al. Diabetes Prevention Program (DPP). *N Engl J Med*.2002;346(6):393-403.
467. Lindstrom J, et al. The Finnish Diabetes Prevention Study (DPS) *Diabetes Care*. 2003;26(12):3230-3236.
468. Pan XR, et al. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20(4):537-544.
471. Ramachandran A, et al. The IDPP-1. *Diabetologia*. 2006;49(2):289-297.
472. Chiasson et al. The STOP-NIDDM Trial. *Diabetes Care*. 1998;21(10):1720-1725.

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 intervention[475, 476, 477]

475. Knowler WC, et al. 10-year follow-up of DPP Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.
476. Li G, et al. Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 2008;371(9626):1783-1789.
477. Lindstrom J, et al. 13 years: Finnish Diabetes Prevention Study (DPS). *Diabetologia*. 2013;56(2):284-293.

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)

SLIDE 7

Monitoring

- Annual assessment / monitoring for glucose tolerance status is recommended
- Screening and appropriate management of other modifiable cardiovascular risk factors is suggested

SLIDE 8

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

SLIDE 9

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]

TOPIC

18

Case Study

prevention of type 2 diabetes mellitus

SLIDE 1

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/m^2
Waist circumference 88 cm. BP 140/95 mmHg.
CVS – no cardiomegaly. No other abnormality.

SLIDE 2

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

SLIDE 3

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

SLIDE 4

Q4: What will you do next?

A. OGTT
B. A1c
C. No need anything else, treat with lifestyle modifications

SLIDE 5

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.

SLIDE 6

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.

SLIDE 7

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

SLIDE 8

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/m^2
- Her A1c is still in pre-diabetic range

APPENDIX

1

template for training program

Template for Training Programme
Clinical Practice Guideliines on the Management of Type 2 Diabetes Mellitus 2015

Day 1

Time	Topic	Speaker
8.00-8.30	Registration of Participants	
	Session 1	Chairperson:
8.30-8.45	Welcoming Address, Introduction of the Workshop & Pre-Test Questions	
8.45-9.00	Overview of Type 2 Diabetes Mellitus (T2DM) & Revised CPG for the Management of T2DM 2015	
9.00-9.30	Screening & Diagnosis	
9.30-9.45	Case Presentation	
9.45-10.00	Q & A	
10.00-10.15	Morning Tea Break	
	Session 2	Chairperson:
10.15-10.30	Targets for Control	
10.30-10.45	Case Presentation	
10.45-11.30	Medical Nutrition Therapy & Low Glycaemic Index Diet	
11.30-11.45	Case Presentation	
11.45-12.00	Physical Activity	
12.00-12.15	Case Presentation	
12.15-12.30	Q & A	
12.30-14.30	Lunch & Friday Prayer	
	Session 3	Chairperson:
14.30-15.15	Oral Anti-Diabetic Medications (Treatment Algorithms, Patient Specific Algorithms etc)	
15.15-15.30	Case Presentation	
15.30-16.15	Insulin Therapy & Non-Insulin Injectables (GLIP-1 RA)	
16.15-16.30	Case Presentation	
16.30-16.45	Q & A	
16.45-17.00	Afternoon Tea Break	
	Session 4	Chairperson:
17.00-17.15	Diabetes with Hypertension	
17.15-17.30	Case Presentation	
17.30-17.45	Diabetes with Dyslipidemia	
17.45-18.00	Case Presentation	
18.00-18.15	Diabetes with Obesity	
18.15-18.30	Case Presentation	
18.30-18.45	Q & A	
18.45	End of First Day Session	

Day 2

Time	Topic	Speaker
	Session 5	Chairperson
8.30-9.00	Management Of Diabetic Emergencies 1: Hypoglycaemia	
9.00-9.15	Case Presentation	
9.15-9.45	Management Of Diabetic Emergencies 2: DKA & HHS	
9.45-10.00	Case Presentation	
10.00-10.30	Management of Chronic Complications 1: Nephropathy, Retinopathy & Neuropathy	
10.30-10.45	Case Presentation	
10.45-11.00	Q & A	
11.00-11.15	Tea break	
	Session 6	Chairperson:
11.15-11.45	Management of Chronic Complications 2: IHD, CVA, Diabetic Foot & ED	
11.45-12.00	Case Presentation	
12.00-12.30	Diabetes in Special Populations 1: Hyperglycaemia in Pregnancy	
12.30-12.45	Case Presentation	
12.45-13.00	Q & A	
13.00-14.00	Lunch	
	Session 7	Chairperson:
14.00-14.30	Diabetes in Special Populations 2: Ramadan & Elderly	
14.30-14.45	Case Presentation	
14.45-15.00	Diabetes in Special Populations 3: Adolescents & Children	
15.00-15.15	Case Presentation	
15.15-15.45	Prevention of Type 2 Diabetes Mellitus	
15.45-16.00	Case Presentation	
16.00-16.15	Q & A	
16.15-16.30	Closing Remarks & Post-Test Questions	
16.30-16.45	Afternoon Tea	
16.45	End of Final Day Session	

APPENDIX

2

pre-test & post-test questionnaire

PRE-TEST & POST-TEST QUESTIONNAIRE

IMPLEMENTATION OF THE CLINICAL PRACTICE GUIDELINE IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS (5th Edition) 2015

SELECT the best answer for each question on the enclosed answer sheet.

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 standardised 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 m^2)
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 m^2.
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 - canaglifozin
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/m^2 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/m^2. 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

Name: _____	Pre-Test	☐
	Post-Test	☐

ANSWER SHEET: PRE-TEST & POST-TEST QUESTIONNAIRE

IMPLEMENTATION OF THE CLINICAL PRACTICE GUIDELINE IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS (5th Edition), 2015

CIRCLE the best answer for each question.

Question No.					
1	A	B	C	D	E
2	A	B	C	D	E
3	A	B	C	D	E
4	A	B	C	D	E
5	A	B	C	D	E
6	A	B	C	D	E
7	A	B	C	D	E
8	A	B	C	D	E
9	A	B	C	D	E
10	A	B	C	D	E
11	A	B	C	D	E
12	A	B	C	D	E
13	A	B	C	D	E
14	A	B	C	D	E
15	A	B	C	D	E
16	A	B	C	D	E
17	A	B	C	D	E
18	A	B	C	D	E
19	A	B	C	D	E
20	A	B	C	D	E
21	A	B	C	D	E
22	A	B	C	D	E
23	A	B	C	D	E
24	A	B	C	D	E
25	A	B	C	D	E

ANSWERS

PRE-TEST & POST-TEST QUESTIONNAIRES

IMPLEMENTATION OF THE CLINICAL PRACTICE GUIDELINE IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS (5th Edition) 2015

Question No.					
1					E
2			C		
3			C		
4					E
5				D	
6	A				
7			C		
8		B			
9	A				
10			C		
11			C		
12				D	
13		B			
14			C		
15			C		
16					E
17					E
18					E
19		B			
20			C		
21			C		
22				D	
23	A				
24			C		
25			C		

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5TH EDITION

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ACADEMY OF MEDICINE MALAYSIA

DIABETES MALAYSIA

FAMILY MEDICINE SPECIALISTS ASSOCIATION OF MALAYSIA

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