Type 1 & 2 Diabetes Mellitus

Objectives :

Type 1 DM:

- ★ Understand diabetes epidemiology in Saudi Arabia
- ★ Demonstrate physiology of insulin action
- ★ Demonstrate pathophysiology of T1DM
- ★ Differentiate treatment options for T1DM

Type 2 DM:

- ★ Explain the nature of type 2 diabetes mellitus
- ★ Know how to make the diagnosis in adults and pregnant
- ★ Gain knowledge in the pathophysiology / females
- ★ Gain knowledge in epidemiology and prevention
- ★ Be familiar with concepts of management including pharmacotherapy

MED439

Medicine Team 439

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Editing file

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Original text
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Extra

Lecture Outline:

★ Intro

- **Insulin**
- **Classification of DM**
- **Clinical features of DM**
- **Investigation**

★ Type 1 DM

- **Definition**: immune-mediated β cell destruction, usually leading to absolute insulin deficiency.
- **Epidemiology:** Accounts for 5-10% of all DM
- **Pathogenesis:** Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion. Autoimmune process is believed to be triggered by environmental factors
- **Risk factors:** Genetics + Environmental
- **Diagnosis :** →

Table 2 – American Diabetes Association diagnostic criteria for diabetes[15]

Test[a]	Threshold	Qualifier
Hemoglobin A_{1c} or	≥ 6.5%	Lab NGSP-certified, standardized DCCT assay
Fasting glucose or	≥ 126 mg/dL (7.0 mmol/L)	No caloric intake for at least 8 hours
2-hour glucose or	≥ 200 mg/dL (11.1 mmol/L)	After 75 g of anhydrous glucose
Random glucose	≥ 200 mg/dL (11.1 mmol/L)	Plus classic hyperglycemia symptoms or crisis

NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial.
[a] Results must be confirmed by repeated testing.

- **Management:** Insulin is always indicated in people with type 1 diabetes

★ Type 2 DM **You can check the Dr's slides for more info regarding (pathogenesis & complications)**

- **Definition**: Ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2o to β cell dysfunction
- **Etiology:** Multifactorial (Diet, age, Obesity, Physical inactivity, Genetics, others)
- **Pathogenesis:** 1. Abnormal insulin action 2. Abnormal insulin secretion
- **Diagnosis:** Same as Type 1
- **Management:**
  - Diet & Lifestyle modification
  - Oral Hypoglycemic drugs
  - Bariatric Surgery

Introduction

Blood glucose is tightly regulated and maintained within a narrow range by insulin & glucagon. This is essential for ensuring a continuous supply of glucose to the central nervous system.

Insulin: the primary regulator of glucose metabolism and storage is secreted from pancreatic β- cells into the portal circulation in response to a rise in blood glucose. The cleavage of proinsulin (precursor molecule of insulin) produces C-peptide (connecting peptide) and insulin.

- After ingestion of a meal containing carbohydrate, normal blood glucose levels are maintained by:
  - Suppression of hepatic glucose production.
  - Stimulation of hepatic glucose uptake.
  - Stimulation of glucose uptake by peripheral tissues.

Insulin secretion in response to a glucose stimulus classically occurs in two phases (Biphasic):

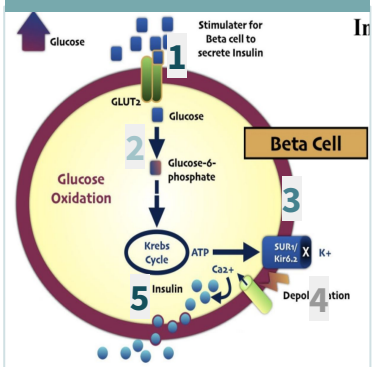
- The **rapid first phase** represents the secretion of pre-formed insulin from granules within the β cell. Mainly helps to prevent postprandial hyperglycemia
- **Prolonged second phase** is a consequence of newly synthesised insulin. It lasts over 1-2 hours until the blood glucose returns to normal

Incretins are amino acids and hormones such as **glucagon-like peptide 1 (GLP-1) and gastrointestinal peptide (GIP)** , released from the small intestines following food intake and can augment insulin release. As a result, insulin release is greater when glucose is administered by mouth than when the same rise in plasma glucose is achieved by intravenous glucose infusion, a phenomenon termed the **(incretin effect)**.

◀ Insulin secretion and action

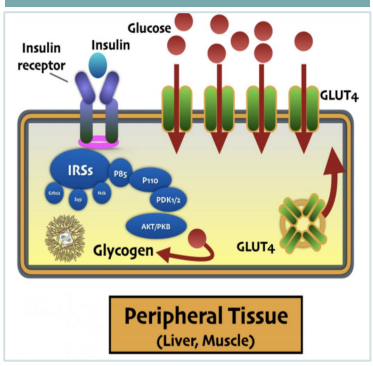
EXTRA

A.In Beta cells



1. Glucose enters Beta cell through facilitated diffusion mediated by **GLUT2** (it is insulin independent)
2. Glucose get phosphorylated by glucokinase and enters Krebs cycle (Glycolysis) to produce ATP
3. ATP **closes** potassium channels that normally secrets K out
4. Potassium increases intracellularly which will cause **Depolarization**
5. **Ca channel opens** (Voltage gated channel), Ca enters the cell leading to the release of insulin from its vesicles by exocytosis

B.In Peripheral tissue



- Insulin & insulin-like growth factor binds to receptor and according to cell needs it activate either one of two pathways:

Growth signal

- Cell proliferation
- Tissue development & differentiation

Metabolic signal:

- Regulation of energy metabolism (Glucose)
- It helps expressing GLUT4 to the cell membrane which facilitate glucose entrance.
- Glucose get converted to glycogen for storage

Introduction

◀ The physiology of insulin action

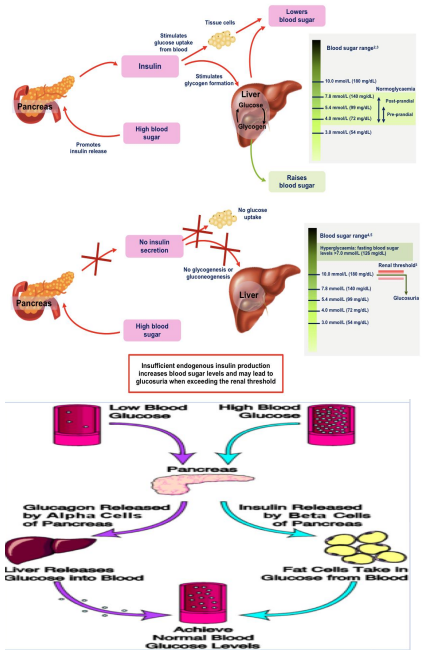
When The Level of Glucose is:

High

- **Hormone**: **Insulin** (Anabolic hormone)
- ↑ glycolysis
- ↑ ion uptake especially K and PO_4^{3-}
- ↓Ketogenesis
- Effect on **Liver**:
1. ↑ Glycogen synthesis
2. ↓ Gluconeogenesis
3. ↓ Glycogenolysis
4. ↑ lipogenesis (FA synthesis)
5. ↑ Lipoprotein synthesis

- Effect on **Muscles**:
1. ↑ protein synthesis
2. ↓ Proteolysis

- Effect on **Adipose tissue**:
1. Inhibition of intracellular lipase > No lipolysis
2. ↑ TGs deposition



Low

- **Hormones**:
1. Glucagon (Mainly)

Other Counter regulatory hormones:

2. Glucocorticoids
3. Growth hormone
4. Epinephrine

- Effect on **Liver**:
1. ↓ Glycogen synthesis
2. ↑ Gluconeogenesis
3. ↑ Glycogenolysis

- Effect on **Muscles**:
1. ↓ protein synthesis

- Effect on **Adipose tissue**:
1. No inhibition of intracellular lipase > ↑ lipolysis > ↑ FFA

◀ Classification of diabetes

	Type 1 DM (Acute presentation)	Type 2 DM (Chronic presentation)
Pathogenesis	due to **β- cell destruction**, leading to absolute insulin deficiency	due to a **progressive insulin secretory defect** on the background of insulin resistance, Caused by obesity mainly
Age and genetics	Usually <30y/o : **HLA-DR3 or DR4**	Usually >30y/o: No HLA links but strong familial predispositions
Weight	20% may be overweight/obese	Virtually all BMI > 85%th percentile
Course	Rapid From DPT-I can be indolent	Indolent Virtually none found on screening
DKA (diabetic ketoacidosis)	35%-40%	Ketonuria (33%) Mild DKA (5%-25%)
Relative with DM	5% with T1DM Up to 30% may have with T2DM FH of T2 2-3Xs in person with T1	74%-100% - 1st–2nd degree with T2DM
Comorbid	**Thyroid, adrenal, vitiligo, celiac**	**Increase in polycystic ovary syndrome, Acanthosis nigricans**
C- peptide Used to differentiate between T1DM and T2DM	C-peptide can be preserved at DX , eventually it will disappear	Normal or increased (more useful in T2)
Antibody	85%	15% (reported as high as 30%)
Ethnicity	Whites predominate	NA, AA, HA, Asian, Pacific Islander

Introduction

◀ Classification of diabetes cont'

Gestational diabetes mellitus (GDM)

- Diabetes diagnosed in the **second or third trimester of pregnancy** that is not clearly overt diabetes
- After delivery blood glucose will return to normal. Each time they become pregnant there will be a 10% more risk for developing permanent DM

Specific types of diabetes due to other causes:

- **Monogenic diabetes syndromes:**
  - Such as neonatal diabetes and maturity-onset diabetes of the young [**MODY**] , which develops under the age of 25 years, and neonatal diabetes that presents during first 6 months of life.
- **Diseases of the exocrine pancreas:**
  - Such as cystic fibrosis
- **Drug or chemical induced diabetes:**
  - Such as in the treatment of HIV/AIDS or after organ transplantation
  - E.g. SLE or RA due to steroids treatment (Improving the primary disease will solve the problem)

◀ Clinical features

1 Acute presentation

- Children and young adults often present with a **2–6-week history** of the **classic triad of symptoms:**

Polyuria
due to the osmotic diuresis that results when blood glucose levels exceed the renal threshold

Thirst and polydipsia
Physiological response to diuresis to maintain plasma volume

Weight loss
due to fluid depletion and accelerated breakdown of fat and muscle secondary to insulin deficiency.

2 Subacute presentation

The clinical onset may be prolonged over **several months or years**, particularly in older people. **Thirst**, **polyuria** and **weight loss** are usually present, but the individual may complain of other symptoms such as **lack of energy**, **visual blurring** secondary to swelling of lens due to osmosis caused by hyperglycemia (owing to glucose- induced changes in refraction), or **pruritus vulvae** or **balanitis** (inflammation of the glans, or the head, of the penis) **due to Candida infection.** Because Candida albicans thrives under increased glucose conditions

3 Complications

Complications as the presenting feature These include:

- **Staphylococcal skin** infections
- **Retinopathy** noted during a visit to the optician (Retinal Screening is recommended at the time of diagnosis of type 2 and after 5 years in type 1)
- **Polyneuropathy** causing tingling and numbness in the feet
- **Erectile dysfunction**
- **Arterial disease,** resulting in myocardial infarction or peripheral gangrene (non-traumatic amputation

Introduction

4 Asymptomatic

Asymptomatic diabetes It is estimated that approximately **half of people with diabetes are unaware** of their condition. up to one- third of diagnoses are made as an **incidental finding** and several countries have introduced screening programmes to identify those with asymptomatic undiagnosed diabetes.

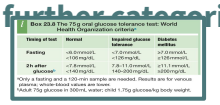
◀ Investigations

Once considered, diabetes is easy to diagnose.
The diagnostic approach is the same for both T1 & T2

- Indications for testing:
  - all symptomatic patients
  - Asymptomatic patients with any of the following characteristics:
    >45 years of age, History of pre-diabetes or gestational diabetes, Obese patients
- **This may be by a laboratory measurement of:**

1. fasting plasma glucose (**FPG** >120) **(Specific)**
2. (random glucose>200) **(Sensitive)**
3. 2-hour plasma glucose after a 75- g oral glucose tolerance test (**OGTT**>200) **(Sensitive & Specific)**
4. The use of glycated haemoglobin (**HbA1c**>6.5)was introduced as an alternative method in 2011. it is also used to guide treatment decisions.

- The diagnostic criteria recognize **two further categories of abnormal** glucose concentrations:



1. impaired fasting glycaemia (**IFG**)
2. impaired glucose tolerance (**IGT**)

- Collectively these have been described as **'pre-diabetes'** but this is not strictly accurate because the majority will never develop diabetes. (⅓ will develop DM)
- Neither IFG nor IGT are clinical entities in their own right but they identify **people who are at high risk of diabetes and cardiovascular disease.**
- Individuals with **IGT** have a similar **risk of cardiovascular disease** as those with frank diabetes, but do not develop **microvascular complications**.

Table 2 – American Diabetes Association diagnostic criteria for diabetes[18]

Test[a]	Threshold	Qualifier
Hemoglobin A_{1c} or	≥ 6.5%	Lab NGSP-certified, standardized DCCT assay
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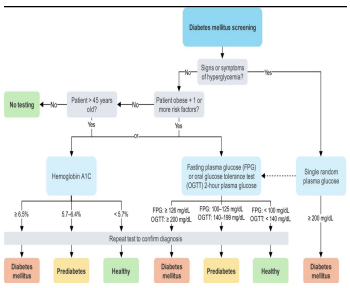
NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial.
[a] Results must be confirmed by repeated testing.

This criteria will diagnose DM but will not differentiate between T2DM and T1DM.
One abnormal laboratory value is diagnostic in symptomatic individuals; two values are needed in asymptomatic people. The glucose tolerance test is only required where there is diagnostic uncertainty and for diagnosis of cystic fibrosis-related diabetes and gestational diabetes.



IFG and IGT are associated with insulin resistance syndrome or syndrome X:

- insulin resistance
- Hyperinsulinemia
- Obesity
- Dyslipidemia (High triglycerides and\or low HDL)
- Hypertension

Introduction

Glycosuria:

- Cannot be used to diagnose diabetes, but requires further investigation.
- It is commoner in older people, who have an altered renal threshold for glucose.
- It may also occur in familial renal glycosuria, which is a monogenic disorder affecting function of the sodium–glucose co- transporter (SGLT2) and found in about 1 : 400 of the population.

- **Other investigations:**
  - No further tests are needed to diagnose diabetes, but measurement of C-peptide and islet autoantibodies can help determine the type of diabetes.
  - C- peptide can be measured in blood or urine; it is often present when type 1 diabetes is diagnosed but disappears with time and is a more useful investigation in people with a duration of diabetes longer than 5 years.
- **Routine investigations:**
  - include urine testing for protein, a full blood count, urea and electrolytes, liver biochemistry and random lipids.
- **Secondary causes:**
  - Investigations of secondary causes of diabetes or associated autoimmune disease may be appropriate

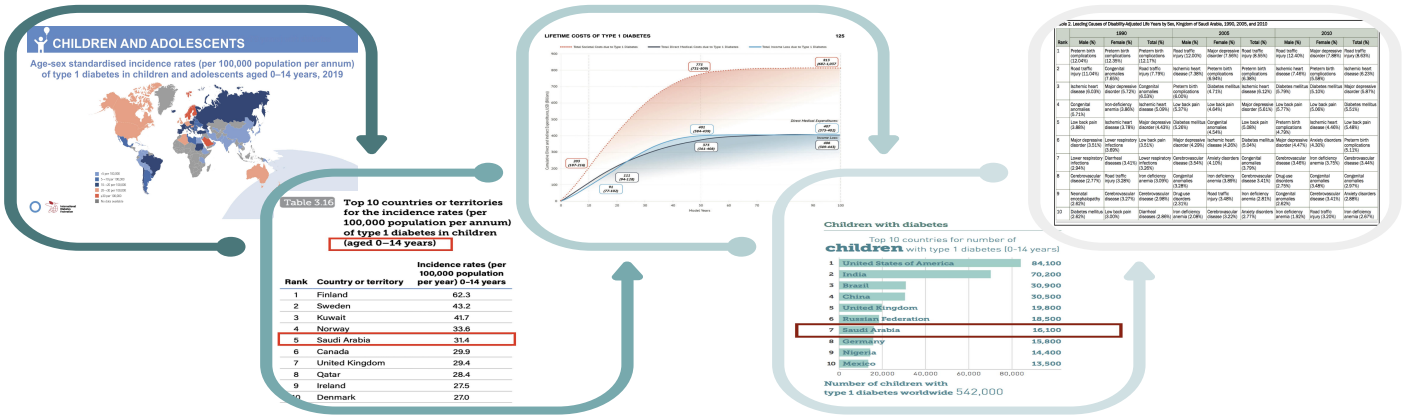
Type 1 DM

◄ What is Diabetes ?

- Diabetes is a complex, chronic illness requiring continuous medical care with **multifactorial risk-reduction strategies beyond glycemic control.** Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications.

◄ DM Epidemiology and Burden

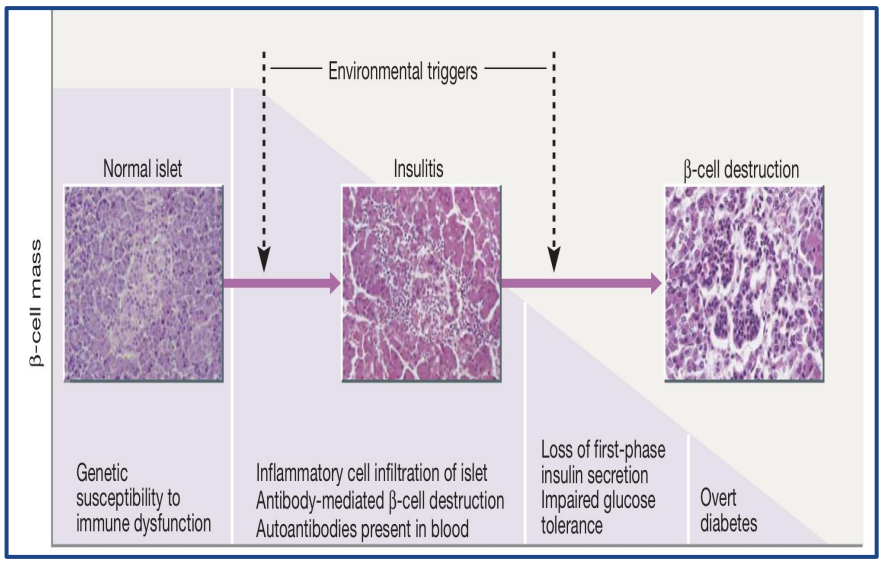
- Diabetes was the **7th leading cause of death** in 2010 behind Ischemic heart disease (1st leading cause) and chronic Kidney disease (6th leading cause). Recall DM increases the risk of IHD and CKD.
- Type 1 diabetes is a disease of insulin deficiency and accounts for 5–10% of all cases of diabetes. It typically presents in childhood and young adulthood, reaching a peak incidence around the time of puberty, but can present at any age.



Type 1 DM

Pathogenesis

- T1DM is the result of interactions of **genetic**, **environmental**, and **immunological factors** that ultimately lead to the **destruction of the pancreatic Beta cells and insulin deficiency**.
- It can develop at any age, but **most commonly < 30**
- Type 1 diabetes is associated with other organ-specific autoimmune diseases including **autoimmune thyroid disease**, **coeliac disease**, **Addison's disease** and **pernicious anaemia**.
- The precise molecular mechanisms that lead to type 1 diabetes are incompletely understood but involve the triggering of a selective autoimmune destruction (Most, but **not all**, individuals have evidence of islet-directed **autoimmunity**) of the insulin producing cells of a genetically predisposed individual.
- Initially, autoantibodies directed against pancreatic islet constituents appear in the circulation and often predate clinical onset by many years.
- **The islet antigens include:**
  - insulin itself, the enzyme glutamic acid decarboxylase (GAD), protein tyrosine phosphatase (IA-2, also known as ICA512), the cation transporter ZnT8 and tetraspanin 7.
- This is followed by a phase of **asymptomatic loss of β cell secretory capacity**:
  - histologically, this is characterized by a chronic inflammatory mononuclear cell infiltrate of **T lymphocytes** and macrophages in the islets, known as **insulitis** . Eventually, when the remaining β cells are no longer able to produce enough insulin to meet the body's needs, diabetes symptoms start to develop.



Type of Diabetes	Normal glucose tolerance	Hyperglycemia: Pre-diabetes* — Impaired fasting glucose or impaired glucose tolerance	Hyperglycemia: Diabetes Mellitus — Not insulin requiring	Insulin required for control	Insulin required for survival
Type 1					
Type 2					
Other specific types					
Gestational Diabetes					
Time (years)					
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)		
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)		
HbA1C	<5.6%	5.7–6.4%	≥6.5%		

Note that T1DM arrow is uni-directional and has rapid onset (unlike T2DM which has indolent course). T1DM pts need insulin for SURVIVAL unlike T2DM.

Quick Recap

- Insulin is anabolic Hormone
- T1DM is genetic predisposition .ex (**HLA-DR3 or DR4**) , result in B cell destruction and insulin deficiency
- T2DM caused by **obesity** mainly, result in Insulin Resistance
- When do T2DM symptoms appear? When the patient loses ⅔ of the Beta cell mass
- Symptoms are the same in both types of Diabetes
- FPG and HBA1C are the most specific Diagnostic Tests

Type 1 DM

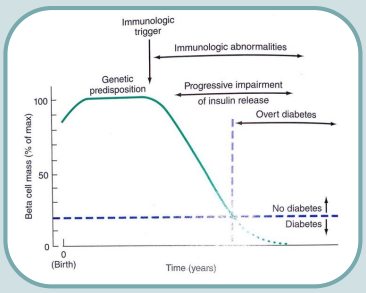
◀ Risk factors

Genetics

- Increased susceptibility to type 1 diabetes is inherited but the disease is not genetically predetermined. The **identical twin** of a person with type 1 diabetes has a **30–50%** chance of developing the disease, which implies that non- genetic factors must also be involved.
- The risk of developing diabetes by age 20 years is greater with a **father** with diabetes **(5–7%)** than with a **mother** with diabetes **(2–5%)**.
- If **one child in a family** has type 1 diabetes, each **sibling** has a **4–6%** risk of developing diabetes.
- This risk rises to about **20%** in **siblings** with the same human leukocyte antigen (**HLA**) genotype as the proband.
- HLA genes are highly polymorphic and modulate the body's immune defence system.
- **More than 90% of people with type 1 diabetes carry HLA- DR3-DQ2, HLA- DR4-DQ8 or both**, as compared with some 35–40% of the background population. By contrast, certain HLA alleles confer **protective effects, for example DQB1*0602.**

Environmental

- Maternal factors, such as gestational infection and older age
- Viral infections, including enteroviruses such as **Coxsackie B4**
- Exposures to dietary constituents, such as early introduction of cow's milk and relative deficiency of vitamin D
- Environmental toxins e.g. alloxan, Vacor
- Childhood obesity
- Psychological stress.



◀ Presentation

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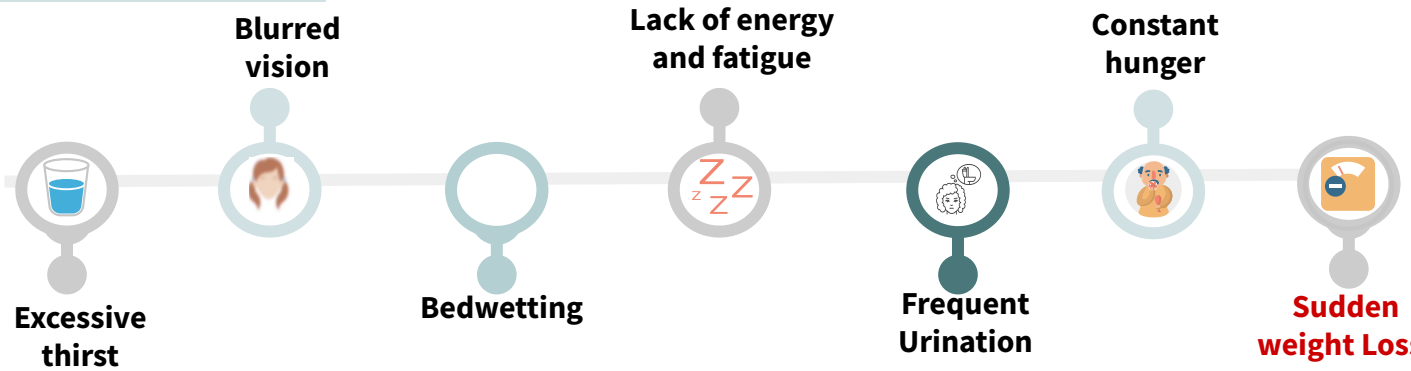

◀ Diagnosis

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Table 2 – American Diabetes Association diagnostic criteria for diabetes[18]

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NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial.
* Results must be confirmed by repeated testing.

1-Sudden weight loss is **more specific for T1DM**, the reason behind this is that T1DM pts are insulin deficient (Recall that insulin has an anabolic effect). T2DM may also present with weight loss but this would occur very late, unlike T1DM which presents from the beginning.

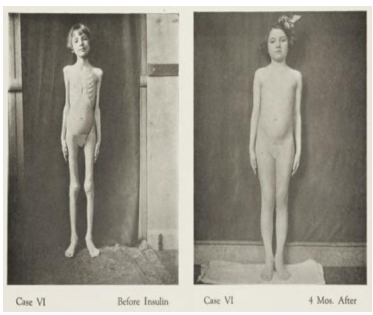
Type 1 DM

◀ Management

◀ Goals of therapy

Through appropriate meds and education

- Eliminate symptoms related to hyperglycaemia
- Reduce risk or eliminate diabetes complications such as diabetic ketoacidosis and hypoglycaemia with effective management when they do occur.
- Allow patient to achieve as **normal lifestyle as possible**
- Avoidance of iatrogenic side-effects,such as hypoglycaemia.
- Regular physical activity, healthy diet, fast and long acting insulin are necessary in treating T1DM



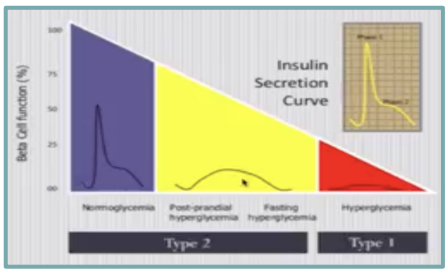
Insulin treatment allows for a dramatic recovery in patients with Type 1 diabetes
With insulin treatment there is weight gain because of the ability of the tissues to use glucose

◀ Insulin is necessary for survival

- Type 1 diabetes is an autoimmune disease leading to β-cell destruction, lack of insulin production and a need for life-long insulin therapy. Insulin is always indicated in people with type 1 diabetes and is often needed in those with type 2 diabetes as the condition progresses.
- Until 1922, the treatment for Type 1 diabetes was a 'starvation diet' – reducing patients to emaciation and subjecting them to a life of misery.
- Prior to discovery of insulin in 1921, the life expectancy of people with type 1 diabetes was only 3–4 months.
- The work of John Macleod, Frederik Banting and Charles Best with their patient, Elizabeth Hughes (right), led to the widespread use of insulin injections as a treatment for Type 1 diabetes.
- **The philosophy of insulin therapy is to mimic the normal physiological secretion of insulin as closely as possible. This involves the use of both long-acting insulin to replicate the basal secretion of insulin and short-acting insulin to cover mealtimes.**

◀ Insulin deficiency

- **In type 1 Diabetes:**
  There is a loss of **both** first and second phase of insulin secretion.
- **In type 2 Diabetes:**
  In the **early stage** of the disease there is **loss of the first** phase of insulin secretion. Phase 2 will become wider then it will gradually reduce to reach a stage of severe insulinopenia.



The basal/bolus insulin concept

Basal Insulin	Bolus Insulin (Mealtime or Prandial)
- Suppresses glucose production between meals and overnight - 50% of daily needs	- Limits hyperglycemia after meals - Immediate rise and sharp peak at 1 hour - 10% to 20% of total daily insulin requirement at each meal

Type 1 DM

Management cont'

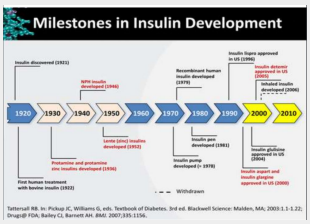
Types of insulin				
Insulin type (trade name)	**Onset**	**Peak**	**Duration**	**Characteristics**
Bolus (preprandial or mealtime) insulins				
Rapid-acting insulin analogues (clear) • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra®) • Insulin lispro (Humalog®) U-100 U-200 • Faster-acting insulin aspart (Fiasp®)	9-20min 10-15min 10-15min 4min	1-1.5h 1-1.5h 1-2h 0.5-1.5h	3-5h 3.5-5h 3-4.75h 3-5h	Enter the circulation **more rapidly than human soluble insulin**, and also **disappear more rapidly.** -5-10 minutes before meal -Used in ER in Case of DKA
Short-acting insulins (clear) • Insulin regular [Humulin®-R, Novolin® ge Toronto] • Insulin regular (Entuzity® (U-500)	30min 15min	2-3h 4-8h	6.5h 17-24h	The use of short- acting insulin analogues in people with type 1 diabetes **reduces total and nocturnal hypoglycaemic episodes** and improves glycaemic control as judged by postprandial glucose concentrations and HbA1c. Used for **pre-meal injection in multiple dose regimens**, during **medical emergencies**, and in patients using insulin pumps. -Can be used by pregnant women
Basal insulins				
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn (Humulin® -N, Novolin® ge NPH)	1-3h	5-8h	Up to 18h	Has the advantage that it **can be premixed** with soluble insulin to form stable mixtures (biphasic insulins). Its use is hampered by variability from one injection to another, the need to resuspend the insulin prior to injection and a peak action, which generally occurs in the middle of the night.
Long-acting insulin (clear) • Insulin detemir (Levemir®) • **Insulin glargine U-100 (Lantus®)** • Insulin glargine U-300 (Toujeo®) • Insulin glargine biosimilar (Basaglar®) • Degludec U-100, U-200 (Tresiba®)	90min	Not applicable	U-100 glargine 24h, detemir 16–24h U-300 glargine >30h degludec 42h	Long- acting insulin analogues **reduce hypoglycaemia** for people with **both type 1 diabetes and type 2 diabetes**, particularly at night.
Premixed insulins[1]				
Premixed regular insulin –NPH (cloudy) • Humulin 30/70 • Novolin® ge 30/70, 40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin			
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (NovoMix® 30) • Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)	(% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)			

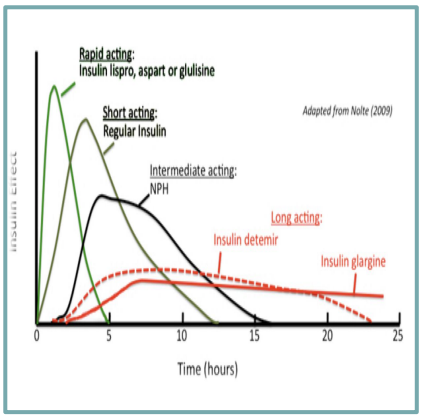
1- Not preferred for T1DM, although it may have some indication in pediatric. We also give premixed insulin in T2DM in case uncontrolled diabetes and Hb1c >10

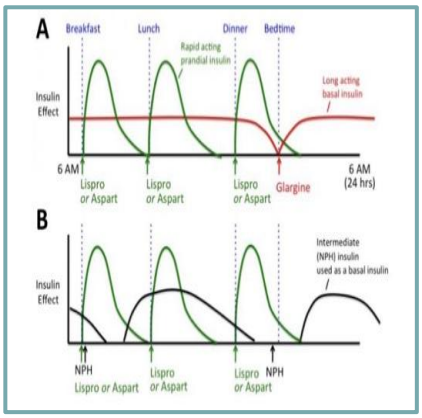
◀ Management cont'

◀ Available Therapeutic Regimens

1. **CT = Conventional Therapy (1 or 2 injections / day)**
   a. Conventional therapy is an old regimen, not recommended anymore, especially for adults (It may have some indications in pediatrics)
2. **MDI = Multiple Daily Injections (3 – 6 injections / day)**
   a. MDI is the **preferred regimen for adults**
3. **CSII = Continuous S.C Insulin infusion "insulin pump " (More flexible)**







Box 23.11 Guide to adjusting insulin dosage according to blood glucose test results

Time	Blood glucose persistently too high	Blood glucose persistently too low
Before breakfast	Increase evening long-acting or pre-mixed insulin	Reduce evening long-acting or pre-mixed insulin
Before lunch	Increase morning short-acting or pre-mixed insulin	Reduce morning short-acting or pre-mixed insulin, or take a mid-morning snack
Before evening meal	Increase morning long-acting or pre-mixed insulin or lunch short-acting insulin	Reduce morning long-acting or pre-mixed insulin or lunch short-acting insulin, or increase mid-afternoon snack
Before bed	Increase evening short-acting or pre-mixed insulin	Reduce evening short-acting or pre-mixed insulin

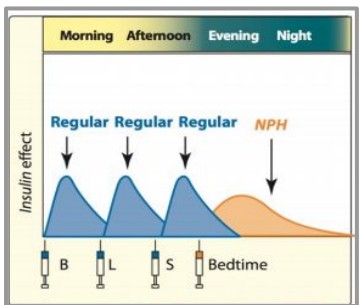
Adjustment should be approximately 10% of the current dose.

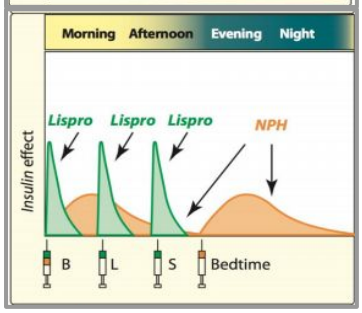
◀ Prandial and basal insulin replacement

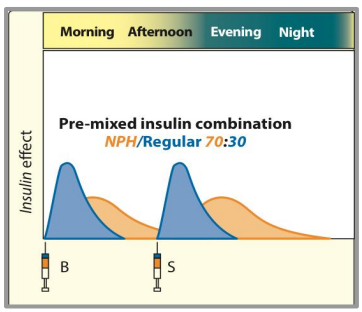
(intermediate & short acting insulin)
Before meals : diabetic patients takes short acting insulin which is regular insulin used to cover the daily need of the insulin after meals.
Before sleeping : no need for strong and fast action because glucose levels before sleeping not high like after meals so, to avoid hypoglycemia and coma the patients takes instead of short acting insulin the insulin intermediate.

(intermediate & Ultra short acting insulin)
Same idea but the short acting insulin is replaced with the ultra-short acting insulin which has a rapid effect As long as the body needs the insulin as a basal level between meals , the patients take double dose of the insulin intermediate to control the glucose level for the whole day not only before meals or sleeping time.

(Insulin mixture(combination) = intermediate + short acting insulin)[4]
Is a helpful drug to reduce the use of injections for the diabetic patients and provide a basal level of insulin during the day and once the patient eat a meal short acting insulin is ready.







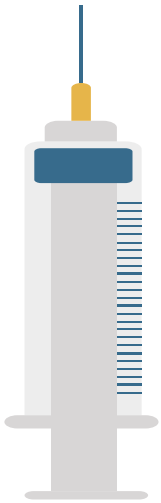
Type 1 DM

◀ Insulin complications

Hypoglycaemia
The most common

Weight gain (overcome by emphasis on the need for diet and exercise, plus addition of metformin)

Insulin antibodies



insulin resistance

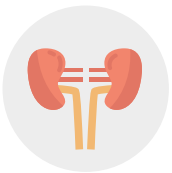
Peripheral oedema (insulin treatment causes salt and water retention in the short term)

Local allergy (rare)

Lipohypertrophy or lipoatrophy at injection sites (result of overuse of a single injection site)

◀ The power of diabetes control

60% less neuropathy



50% less nephropathy

70-76% less retinopathy

◀ Key messages

- **Basal-bolus insulin therapies** (i.e. multiple daily injections or continuous subcutaneous insulin infusion) **are the preferred insulin management regimens for adults with type 1 diabetes.**
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counselled about the risk, prevention treatment of hypoglycemia.
- Avoidance of nocturnal hypoglycemia may include changes in insulin therapy and increased monitoring.
- If glycemic targets are not met with optimized multiple daily injections, continuous subcutaneous insulin infusion may be considered. Successful continuous subcutaneous insulin infusion therapy requires appropriate candidate selection, ongoing support and frequent involvement with the health-care team.
- Continuous glucose monitoring may be offered to people not meeting their glycemic targets, who wear the devices the majority of the time, in order improve glycemic control.

Type 2 DM

◀ Obesity & T2DM in SA much more common than (T1DM)

- Elevated BMI (>25) is associated with an increased risk for the development of type 2 diabetes.
  - Prevalence of type 2 diabetes closely matches the prevalence of obesity.
- The prevalence of overweight was 36.9%.
  - The age-adjusted prevalence of obesity was 35.5% in KSA.
  - **Females** are significantly **more obese** with a prevalence of 44% than males 26.4% .
- The overall prevalence of DM obtained from this study is 23.7% in KSA.
  - The prevalence in males and females were 26.2% and 21.5%
  - Diabetes mellitus was more prevalent among Saudis living in urban areas of 25.5% compared to rural Saudis of 19.5%
  - **27.9% were unaware** of having DM
- Diabetes kills 1 Saudi every 30 minutes, New case diagnosed every 2 MINUTES
- **More deaths than TB and breast cancer combined**[1]
- **Average life expectancy:** 15 years less than non-diabetes population

◀ Etiology

A. Diet:

- Certain dietary patterns are associated with higher or lower risks of type 2 diabetes.
- **Components that increase the risk include:**
  dietary fat, particularly saturated fat, red and processed meat, consumption of fried food, including French fries, increased intake of white rice and sugar-sweetened beverages.
- **The following are associated with lower rates of T2DM:**
  Wholegrains, increased fruit and vegetable intake, fermented dairy products, oily fish and a Mediterra- nean dietary pattern are associated with

B. Ageing:

- Pancreatic **B-cell function declines with age** and the incidence of type 2 diabetes increases with age

C. Obesity:

- Obesity increases the risk of type 2 diabetes up to 80-100-fold and **accounts for 80-85% of the overall risk** of developing type 2 diabetes. A **central distribution of fat** increases the risk of type 2 diabetes, and so for any given level of obesity, **the more visceral fat** an individual has, **the higher the risk** of type 2 diabetes.

D. Fetal origins of diabetes:

- There is a J-shaped relationship between **low weight at birth** and at 12 months of age and glucose intolerance later in life, particularly in those who gain excessive weight in adulthood. The concept is that **poor nutrition early in life impairs B-cell development function**, predisposing to diabetes later on.

E. Physical inactivity:

- Associated with an increased risk of diabetes.

1- But it's not recorded in the death certificate bc it's not the direct cause

Type 2 DM

◀ Etiology cont'

F. Genetic susceptibility and inheritance

- **Identical twins** of people with type 2 diabetes have **more than a 50% chance** of developing diabetes: the risk to **non-identical twins** or siblings is approximately **25%,** confirming a strong inherited component to the disease.
- Most of the identified genetic markers exert very modest risk and **together explain less than 20%** of the heritability of type 2 diabetes.

G. TNF-alpha may induce insulin resistance in obesity from the slides

- The cytokine tumour necrosis factor - ***α*** (TNF- ***α***) is produced from adipose tissue, and TNF-***α*** levels are often elevated in obesity.
- Administration of TNF - ***α*** leads to insulin resistance.
- Over-expression of TNF-***α*** in adipose and muscle of obese, insulin resistant diabetic subjects is positively corrrelated with insulin resistance.
- Polymorphisms at the TNF-***α*** locus correlate with insulin resistance.
- TNF-***α*** inhibits insulin receptor signalling in adipocytes.
- TNF-***α*** deficiency (knockout mice) prevents diet-induced insulin resistance.

H. Other factors

- Other risk factors include urbanization, poverty, abnormal sleep patterns, environmental toxins and mental illness, High-risk ethnic or racial group, Diabetes mellitus in a first-degree relative, History of vascular disease

◀ Pathogenesis

★ **Both defects are necessary** to develop diabetes.

1 Abnormalities of insulin action

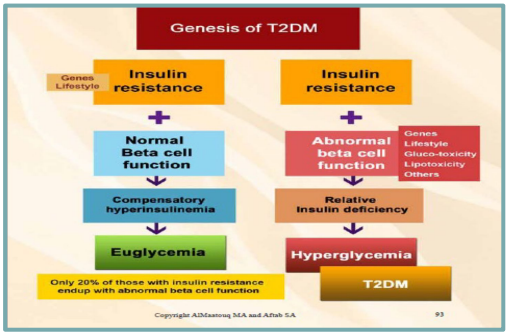
Insulin resistance, which is defined as the inability of insulin to produce its usual biological effects at physiological concentrations. **It is characterized by an impaired ability of insulin to:**

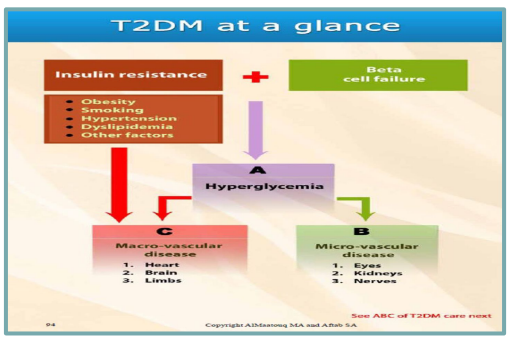
Inhibit hepatic glucose output

Stimulate glucose uptake into skeletal muscle

Suppress lipolysis in adipose tissue.

- The underlying mechanisms of insulin resistance are **not fully understood** but result from nutrient excess.





Hyperglycemia alone will lead to **micro**vascular complications. If combined with other factors (e.g. Obesity, smoking etc.) it will lead to **macro**vascular complications. Microvascular complications causes morbidity and macrovascular causes mortality. You should deal with (B) and (C) **not only (A),** bc for example a pt with retinopathy may become blind in 10yrs, so refer to ophtha early.

Type 2 DM

◄ Pathogenesis cont'

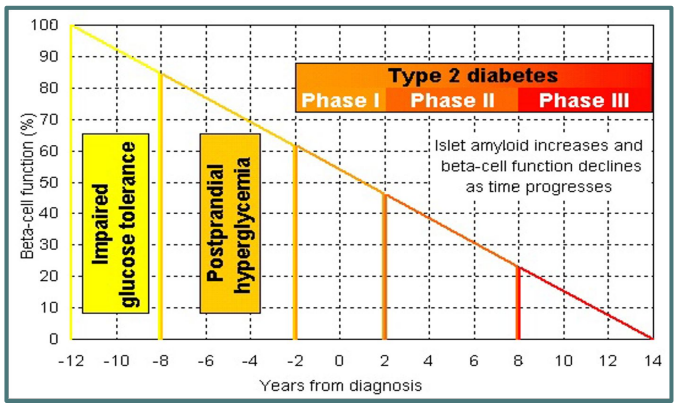
2 Abnormalities of insulin secretion

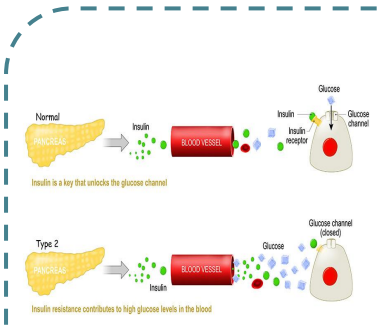
01

- As insulin resistance develops, the body's response is to **increase insulin secretion** and so **early diabetes** is often associated with **insulin hypersecretion**.
- Insulin secretory abnormalities manifest early in the course of type 2 diabetes and progress with time; an **early sign is loss of the first phase of the normal biphasic insulin secretion**.

02

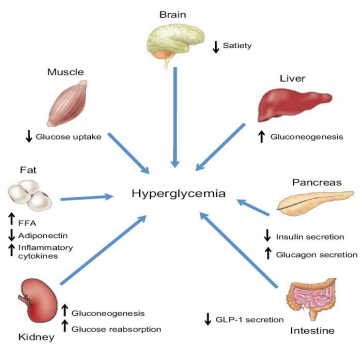
- Even though circulating insulin concentrations are **higher** than in people without diabetes, they are **still inadequate** to restore glucose homeostasis. **By the time of diagnosis, at least 50% of B-cell mass and function has been lost.**
- Hyperglycaemia and lipid excess are toxic to ß cells, at least in vitro, a phenomenon known as **glucotoxicity**, which is thought to cause **further B-cell** loss and further deterioration of glucose homeostasis. With time, insulin secretion declines, an observation referred to as the 'Starling curve' of the pancreas.

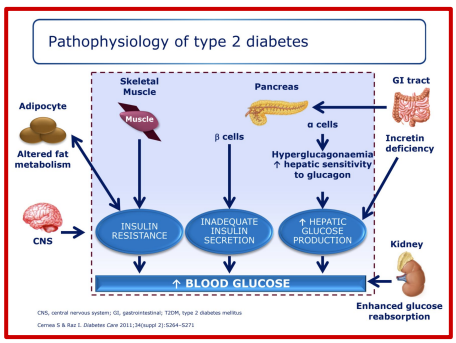




I. **Disrupted pulsatile insulin response**
II. **↓first phase**
III. **↑Proinsulin / insulin ratio**
IV. **↓β-cell responsiveness to glucose**
V. **↓insulin production**
- **↓insulin**
- **↓insulin granules**

Abnormalities of β-cell Function in Type 2 Diabetes





In summary, the pathogenesis of type 2 DM: Relative insulin secretion loss and/or decrease in insulin sensitivity (increase in insulin resistance)

◄ Clinical features

Click here to go back to slide 4

◄ Diagnosis

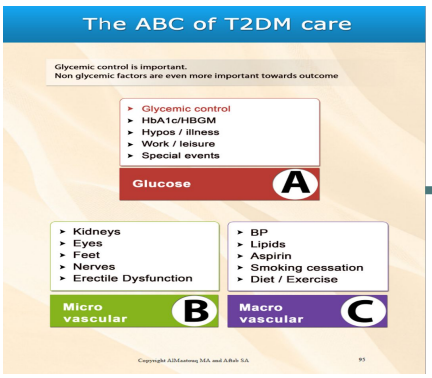
Click here to go back to slide 5

1. **Gold standard for the diagnosis of DM is HbA1C** because it is stable, accurate if done in qualified lab and has no much variability.
2. Retinopathy in DM is unique and can be used as a marker as it is different than other types of retinopathy like in HTN and other diseases.

Type 2 DM

◀ Management of T2DM

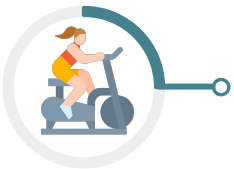
- **Diet and lifestyle** changes are the key to successful treatment of type 2 diabetes. **Medication should never be prescribed until lifestyle changes have been implemented.**
- The three main options are **metformin, a sulfonylurea or a thiazolidinedione.**
- If control is inadequate (if HbA1c > 10%) oral therapy, insulin therapy should be started without undue delay
- DM management depends on hyperglycemia, microvascular complications and macro-vascular together.



Does it work? YES see on the right where treatment has decreased the microvascular complication by about 37% for every 1% decrease in HBA1C

Better control means fewer complications

Every 1% reduction in HBA1C	REDUCED RISK
Deaths from diabetes	21%
Heart attacks	14%
Microvascular complications	37%
Peripheral vascular disorders	43%



Diet & lifestyle modifications:

- All patients with diabetes require healthy diet therapy
- Reducing alcohol consumption and stopping smoking
- Weight management and regular exercise is encouraged to reduce cardiovascular risk
- Exercises increase muscular insulin sensitivity.
- **Dietary advice:**

1. Salad: 1hour BEFORE the meal
2. 1⁄4 - 1⁄2 what you are used to. No cheating. 3. 1 Fruit per meal (juice is fruit)
4. 2 DATES BID (1 extra date BID)
5. No Communal eating
6. Avoid what you can live without.

Oral Hypoglycemic drugs:

HgbA1c targets:

- 7%: Early young without atherosclerosis (AT)
- 8%: Late old
- In diabetic older patients with AT the target of HbA1C is 8% and there is no evidence that 7 better than 8, while in younger patients with no AT the target i

Type 2 DM

Oral Hypoglycemic drugs:

Insulin Sensitizers with predominant action in the liver (Biguanides: metformin)

MOA

- Stimulate skeletal muscle glucose uptake and inhibition of hepatic gluconeogenesis
- increases insulin sensitivity, peripheral glucose utilization and reduces gluconeogenesis

Clinical use

- Metformin is the best-validated treatment for type 2 diabetes and appears as the **first-line pharmacological agent in all type diabetes guidelines.**
- Metformin may be given in combination with other oral diabetes treatments as well as GLP-1 receptor agonists or insulin. It lowers fasting plasma glucose by 2-4 mmol/L (36–72 mg/dL), corresponding to a fall in HbA_1c of 11-22 mmol/ mol (1-2%).
- Metformin has been used alongside insulin in people with **type 1** diabetes but only with **limited efficacy**.

Adverse effects

- **Gastrointestinal side-effects such as:** anorexia, nausea, abdominal discomfort and diarrhoea. the most common. It can also cause vitamin B12 deficiency (decreased absorption).
- The effects can be **mitigated by starting at low dose** and gradually increasing until the desired therapeutic effect is achieved.
- **Contraindicated** in: **renal impairment**, **cardiac failure** and **hepatic failure** because of the risk of **lactic acidosis.**
- Should be stopped temporarily around surgery or during other intercurrent illnesses that may affect lactate clearance.
- Should be **avoided** in people with a history of **alcohol misuse.**
- Should not be started in someone whose estimated glomerular filtrate (EGFR) is less than 45 mL/min per 1.73m^2 and should be stopped if the eGFR falls below 30 mL/min 1.73m^2.
- Does not cause weight gain and it's not associated with with a significant risk of hypoglycemia

Sulphonylureas

Chlorpropamide, Tolazamide, Gliclazide, Glimepiride, Glibenclamide (aka **glyburide) , Glipizide, Tolbutamide**

MOA

- **Act on the B cell to induce insulin secretion.**
- They are ineffective in people without a functional B-cell mass and therefore have **no effect in people with type 1 diabetes.**
- Has a long half-life and has an effect on both pre-prandial and post-prandial

Clinical use

- Most clinical guidelines recommend that sulphonylureas **can be used as an alternative first-line** agent where metformin is contraindicated or not tolerated.
- As monotherapy, sulphonylureas typically reduce fasting plasma glucose by 2–4 mmol/L (36–7 to a fall in HbA,c of 11–22 mmol/mol (1-2%). g/dL), corresponding.

Adverse effects

- **Weight gain**, typically 1-4 kg, and **hypoglycaemia** are the most common side effects.
- The risk of hypoglycaemia is increased with longer acting sulphonylureas, excessive alcohol intake, older age and during intercurrent infection.
- Severe sulphonylurea-induced hypoglycaemia should be managed in hospital for up to 48 hours with glucose support until the drug has cleared from the circulation.
- Contraindicated in renal failure and hepatic failre.
- **Glibenclamide** is best avoided in renal failure and the elderly b/c of its relatively long duration of action (12-20 hours) and renal excretion)

Type 2 DM

Thiazolidinediones : pioglitazone, rosiglitazone

MOA	• **Reduce insulin resistance** by interaction with peroxisome proliferator-activated receptor-gamma (PPAR-Y), a nuclear receptor that regulates large numbers of genes, including those involved in lipid metabolism and insulin action. It leads to an improvement in glycemic control over weeks to months in parallel with an improvement in insulin sensitivity and a reduction in FFA levels.
Clinical use	• Can be used as monotherapy or in combination with other antidiabetic drugs, including insulin. • Thiazolidinediones **do not cause hypoglycemia** as monotherapy. • **Pioglitazone** may specifically **benefit** people with **non-alcoholic fatty liver disease**, a frequent co-morbidity of type 2 diabetes. As the effect on plasma glucose is indirect, thiazolidinediones **may take up to 3 months** to reach their maximal effect.
Adverse effects	• The most common adverse effect is **weight gain** of 5-6 kg. • **Pioglitazone** may cause **fluid retention** (and associated edema formation and hemodilution) **precipitating heart failure.** • Increased risk of bone fractures • May cause anemia and osteoporosis. There is possible increase in risk of bladder cancer. • Contraindicated in pts with active hepatocellular disease and in patients with unexplained serum ALT levels greater than 2.5 times the upper limit of normal

Meglitinides or post-prandial insulin releasers

Repaglinide, Nateglinide

MOA	• Short-acting agents that **promote insulin secretion in response to meals.** Mode of action Like sulphonylureas, meglitinides act by **closing the K*-ATP channel in the ß cells** have a short duration of action of less than 3 hours. • They were designed to **restore early-phase post-prandial insulin release.**
Clinical use	• Meglitinides may be used to treat people with **post-prandial hyperglycaemia** with normal fasting glucose levels. • Suitable for use in diabetic pts with IRF or with renal failure undergoing dialysis
Adverse effects	• **Hypoglycaemia** and **weight gain** are the most common adverse effects but these are generally less severe than with sulphonylureas.

Dipeptidyl peptidase-4 (DPP4) inhibitors or 'gliptins

Sitagliptin, Linagliptin, Vlidagliptin, Alogliptin, Saxagliptin

gliptins are one of two classes of drug that improve glycaemic control by enhancing the incretin effect

MOA	• These drugs **inhibit the enzyme DPP4**, which prevents the rapid inactivation of glucagon-like peptide-1 (GLP-1), which **in turn increases insulin secretion and reduces glucagon secretion**.
Clinical use	• DPP-4 inhibitors are most **effective in the early stages of type 2 diabetes**, when insulin secretion is relatively preserved, and are currently **recommended for second-line use in combination** with metformin or a sulphonylurea. • They're not associated with nausea because of the lesser increase in GLP-1 activity • Weight affect neutral
Adverse effects	• **Contraindication:** history of pancreatitis, and advanced kidney disease (eGFR ,30 mL/minute per 1.73m^2), except linagliptin which can be used. • Occasional reports of **acute pancreatitis**. • **Saxagliptin** may increase the **risk of heart failure and hospitalization**.

Type 2 DM

Sodium-glucose transporter 2 inhibitors ('flozins')

Dapaglilozin ,Empaglilozin, Canaglilozin

In addition to their effects on blood glucose, they lower body weight, improve renal dysfunction and reduce the risk of atherosclerotic cardiovascular events and heart failure.

MOA	• They work by blocking the SGLT2 protein located in the proximal convoluted tubule of the nephron resulting in glycosuria and thereby lowering plasma glucose concentration. • Lower the renal threshold for glucose, consequently **increasing urinary glucose excretion.**lowering blood glucose by 7-13 mmol/mol (0.6-1.2%) and facilitating weight loss • Exactly how SGLT2 inhibitors reduce the risk of myocardial infarction, stroke, cardiovascular death heart failure is uncertain.
Clinical use	• can be used as monotherapy but are used more typically in combination with all other antidiabetes drugs. • Beneficial effect include weight reduction, positive cardiovascular outcome (all cause mortality, nonfatal stroke , and nonfatal MI),and lower hospitalization for heart failure. • This class has become rapidly established in clinical practice and in type 2 diabetes guidelines because of their cardiovascular benefits, weight loss and low risk of hypoglycaemia. SGLT2 inhibitors are licensed as **adjunctive therapy to insulin in type 1 diabetes.**
Adverse effects	• The most common adverse effects are **genital candidiasis and dehydration.** • .Associated with risk of diabetic ketoacidosis, dehydration, increased incidence of genitourinary tract infection “fungal”. • Canagliflozin :- increased risk of fracture and toe amputation.

Alpha-glucosidase inhibitors

Acarbose ,Miglitol ,Voglibose

MOA	• **Prevent a-glucosidase**, the last enzyme involved in carbohydrate digestion, from breaking down disaccharides to monosaccharides. This **slows the absorption of glucose** after a meal and lowers post-prandial glucose.
Clinical use	• Can be used as monotherapy or in combination with all other antidiabetes drugs, they are not widely used because of their limited efficacy and gastrointestinal side-effects. • Doesn’t cause hypoglycemia and it is weight neutral
Adverse effects	• The major side-effects are **gastrointestinal** and include flatulence, abdominal distension and diarrhoea, as **unabsorbed carbohydrate is fermented in the bowel**.

20.26 Effects of drugs used in the treatment of type 2 diabetes

	Insulin	Sulphonylureas and meglitinides	Metformin	Alpha-glucosidase inhibitors	Thiazolidinediones (glitazones)	DPP-4 inhibitors (gliptins)	GLP-1 receptor agonists	SGLT2 inhibitors
Fasting blood glucose	↓	↓	↓	↘	↓	↓	↓	↓
Post-prandial blood glucose	↓	↓	↓	↓	↓	↓	↓	↓
Plasma insulin	↑	↑	↓	↓	↓	↑	↑	↓
Body weight	↑	↑	→	→	↑	→	↓	↓
Cardiovascular benefit?	No	No	Possible	No	Probable (pioglitazone)	No	Yes	Yes
Risk of hypoglycaemia	++	+	–	–	–	–	–	–
Tolerability	Good	Good	Moderate	Moderate	Moderate	Good	Moderate	Limited experience

(↘ = small reduction; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium and glucose transporter 2)

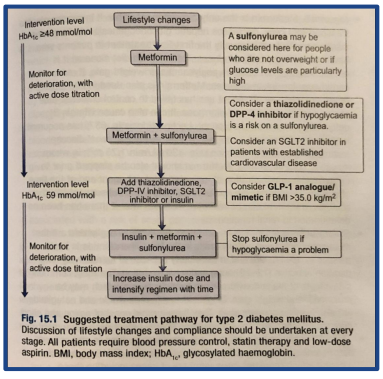


Fig. 15.1 Suggested treatment pathway for type 2 diabetes mellitus. Discussion of lifestyle changes and compliance should be undertaken at every stage. All patients require blood pressure control, statin therapy and low-dose aspirin. BMI, body mass index; HbA_{1c}, glycosylated haemoglobin.

Type 2 DM

GLP-1 receptor agonist

Exenatide: **Twice daily** **2 doses: 5 mg- 10 mg** **weight reduction**	**Liraglutide:** **once daily** **3 doses: 0.6, 1.2, 1.8 mg** **HbA1c :0.8- 1.8**	**Lixisenatide** **Dulaglutide** **Semaglutide** **Albiglutide**

GLP-1 receptors are a heterogeneous class of drugs that act by enhancing the incretin effect.

MOA

- GLP-1 is produced in intestinal L cells and is secreted in response to nutrients
- GLP-1 stimulates insulin secretion in a glucose dependent fashion, inhibits inappropriate hyperglucagonemia, slows gastric emptying, reduces appetite and improves satiety
- It has a very short life in plasma (1 to 2 minutes) due to aminoterminal degradation by the enzyme (DPP4)
- Unlike DPP-4 inhibitors that restore physiological GLP-1 levels, GLP-1 receptor agonists achieve pharmacological levels and are therefore **more potent that DPP-4 inhibitors.** In addition to their effects on the pancreas to increase insulin secretion and decrease glucagon, they also **act on the hypothalamus to reduce appetite and food intake leading to weight loss.** The size of effect has led to the **licensing of liraglutide as an anti-obesity treatment.**

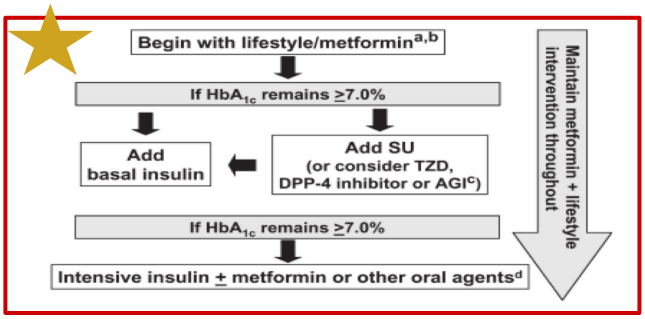
Clinical use

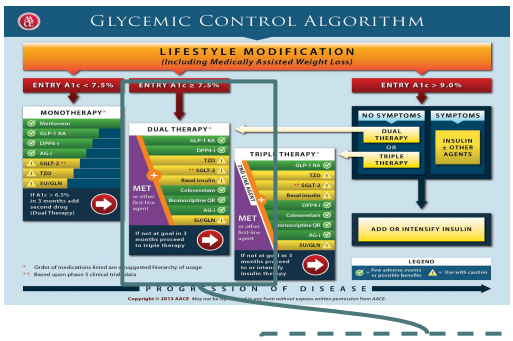
- Despite the need for injection, clinical guidelines endorse their use and GLP-1 receptor agonists are now widely used in combination with other antidiabetic agents, as second- or third-line therapies. They should not be combined with DPP-4 inhibitors as the DPP-4 inhibitor does not confer any additional benefit.
- Beneficial effect include weight reduction, positive cardiovascular outcome (all cause mortality, non fatal stroke, and non fatal MI) and reduction HbA1c

Adverse effects

The most common side-effects of GLP-1 receptor agonists are **gastrointestinal** and include nausea and vomiting, bloating and diarrhoea. There is a low risk of hypoglycaemia but this may occur if GLP-1 receptor agonists are combined with insulin or sulphonylureas. GLP-1 receptor agonists should not be used in people with a history of pancreatitis because of a **risk of acute pancreatitis. It may also induce weight loss (approx. 3-6kg) but most pts will regain the weight once the medication is stopped**

Recommend treatment Algorithm for Middle East





The choice of medication depends on a few things:

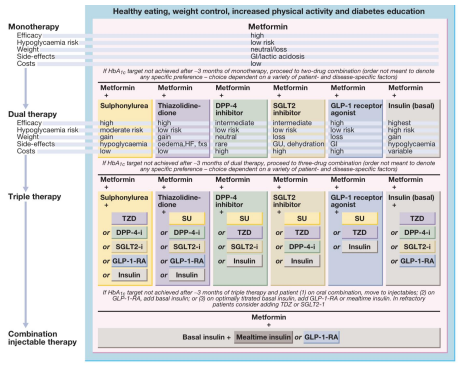
1- Socio-economic status: For example if the pt is a driver then you shouldn't use SUs, insulin. Or if the pt is the one paying for the meds, you shouldn't use expensive drugs. If the pt lives alone or blind then you shouldn't give insulin

2- Presence of vascular complications: For example if you give insulin and they develop hypoglycemia → fall → break their leg, this is probably worse than DM itself.

3- Patient age

4- Disease duration

5- History of hypoglycemia

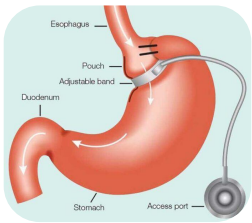
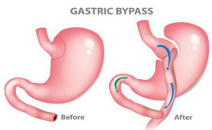
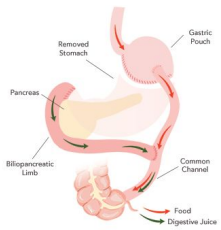


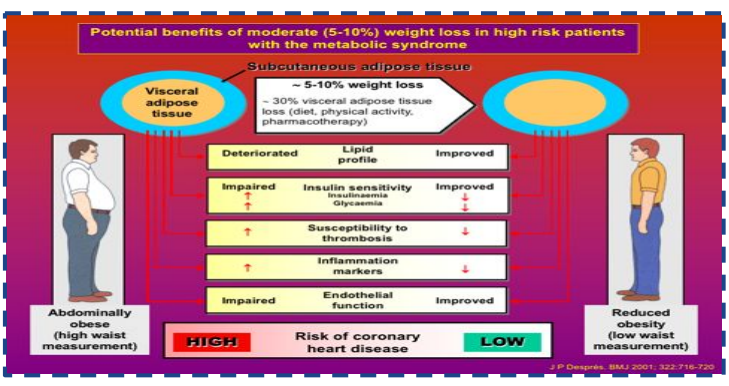
Note that in the triple therapy there are 10 drug groups, and in each group there are at least 4-5 drugs. if you were to choose 3meds from these groups, there will be 1440 possible combination (And it's impossible to determine what fits the pt best).

◄ Management of T2DM cont'

Complications of Bariatric Surgery:

- Bariatric or metabolic surgery is a treatment option for people with severe obesity. The National Institute for Health and Care Excellence (NICE) recommends consideration of surgery in those with a **(BMI) higher than 40 kg/m2** , or in those with a **BMI of more than 35 kg/m 2 and co-morbidities**, such as diabetes.
- **Not recommended, Why?:**
  - Bc it's SURGERY
  - In 5yrs most of the pts will regain all the weight they've lost.
  - It's not effective in those who have been suffering from DM for a long time bc they probably already have extreme insulin deficiency

1- Complications of all Procedures	• Atelectasis and pneumonia • Deep vein thrombosis • Pulmonary embolism • Wound infection • Gastrointestinal bleeding	• Gallstones • Failure to lose weight • Intractable vomiting/kwashiorkor (B1) • Mortality (0.1%–2%)
2- Complications of Gastric banding procedure	• Band slippage • Band erosion • Esophageal dilatation • Band or port infections • Port disconnection • Port displacement	
3- Complications of Gastric bypass	• Anastomotic leak with peritonitis • Stomal stenosis • Marginal ulcers • Staple line disruption 	• Nutrient deficiencies (iron, calcium,folic acid, vitamin B12) • Dumping syndrome • Small bowel obstruction: Internal hernia - Adhesions
4- Complications of Biliopancreatic diversion	• Anastomotic leak with peritonitis • Protein-calorie malnutrition • Calcium, iron, folic acid, fat soluble vitamin (A,D,E,K) deficiencies • Dehydration • Steatorrhea • Small bowel obstruction: Internal hernia - Adhesions	



Box 23.15 Considerations when choosing treatment for type 2 diabetes

Characteristics of the person with diabetes
- Current lifestyle
- Co-morbidities
  - Atherosclerotic vascular disease
  - Heart failure
  - Chronic kidney disease
- Clinical characteristics
  - Age
  - Weight
  - Current HbA_{1c}
- Psychosocial issues such as motivation and depression
- Cultural and socioeconomic context

Specific factor
- Individualized HbA_{1c} target
- Impact on weight and hypoglycaemia
- Medication side-effects
- Treatment complexity
- Choose regimen to optimize medication taking
- Access, cost and medication availability

Shared decision-making
- Involves an educated and informed person with diabetes (and their family/caregiver)
- Seeks patient preferences
- Ensures effective consultation
- Empowers the person with diabetes
- Ensures access to diabetes self-management education

Take home Messages

Type 1:

- Type 1 DM is **often sudden**, while Type 2 DM is **typically gradual**.
- Diabetes type 1 childhood onset typically < 20 years. **Peaks** at age 4–6 years and 10–14 years.
- Weak **familial** predisposition in Type 1. Strong **familial** predisposition in Type 2.
- "If you buy **4 D**ia**M**onds and only pay for **3**, you get **1** for free:" **DR4 and DR3** are associated with **Diabetes Mellitus type 1**. Type 2 DM has no HLA association.
- Classic symptoms (i.e., polyuria, polydipsia, polyphagia, weight loss) are **common** in Type 1 DM, **sometimes** happen in Type 2 DM.
- A thin appearance is typical for patients with T1DM.
- **Gold standard for the diagnosis of DM is HbA1C.**
- **MDI = Multiple Daily Injections (3 – 6 injections / day) is the preferred regimen for adults with Type 1 DM.**
- **The most common complication of insulin use is Hypoglycemia.**

Type2:

- **Obesity accounts for 80-85% of the overall risk** of developing type 2 diabetes
- **The pathogenesis of type 2 DM:** Relative insulin secretion loss and/or decrease in insulin sensitivity (increase in insulin resistance)
- Possible cutaneous signs of insulin resistance:
  - Benign acanthosis nigricans.
  - Acrochordons.
- Diabetes mellitus should be suspected in patients with recurrent cellulitis, candidiasis, dermatophyte infections, gangrene, pneumonia (particularly tuberculosis reactivation), influenza, genitourinary infections (UTIs), osteomyelitis, and/or vascular dementia.
- **Medication should never be prescribed until lifestyle changes have been implemented.**
- **IMP: when you diagnose a pt with DM2 start management with diet & lifestyle modifications and reassess in the next visit. If the HbA1c is still high -> start monotherapy (metformin) & reassess after ~ 3 months.** If there are contraindications for metformin, choose a different noninsulin antidiabetic, depending on patient factors
- The three main options are **metformin (1st line) , a sulfonylurea or a thiazolidinedione.**
- If control is inadequate (if HbA1c > 10%)oral therapy, insulin therapy should be started without undue delay
- DM management depends on hyperglycemia, microvascular complications and macro-vascular together.

Reference: AMBOSS+ Slides.

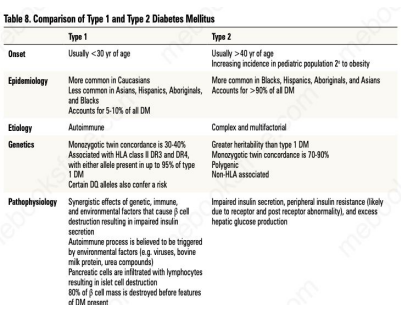


Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Onset	Usually <30 yr of age	Usually >40 yr of age Increasing incidence in pediatric population 2° to obesity
Epidemiology	More common in Caucasians Less common in Asians, Hispanics, Aboriginals, and Blacks Accounts for 5-10% of all DM	More common in Blacks, Hispanics, Aboriginals, and Asians Accounts for >90% of all DM
Etiology	Autoimmune	Complex and multifactorial
Genetics	Monozygotic twin concordance is 30-40% Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of type 1 DM Certain DQ alleles also confer a risk	Greater heritability than type 1 DM Monozygotic twin concordance is 70-90% Polygenic Non-HLA associated
Pathophysiology	Synergistic effects of genetic, immune, and environmental factors that cause β-cell destruction resulting in impaired insulin secretion Autoimmune process is believed to be triggered by environmental factors (e.g., viruses, bovine milk protein, urea compounds) Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction 80% of β-cell mass is destroyed before features of DM present	Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormality), and excess hepatic glucose production

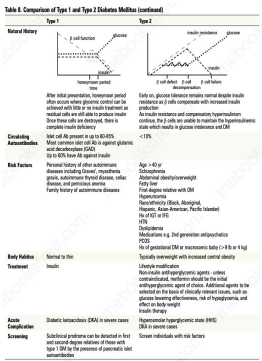


Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)

	Type 1	Type 2
Natural History	β-cell function, glucose hemolysmen period time insulin	insulin resistance, glucose insulin β-cell defect, β-cell decompensation, β-cell failure After initial presentation, honeymoon period often occurs when glycemic control can be achieved with little insulin because residual cells are still able to produce insulin. Once these cells are destroyed, there is complete insulin deficiency.	Early on, glucose tolerance remains normal despite insulin resistance as β-cells compensate with increased insulin secretion. As insulin resistance and compensatory hyperinsulinism continue, the β-cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM
Circulating Autoantibodies	Islet cell Ab present in up to 80-85% Most common islet cell Ab is against glutamic acid decarboxylase (GAD) Up to 60% have Ab against insulin	<10%
Risk Factors	Personal history of other autoimmune diseases including Graves', myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia Family history of autoimmune diseases	Age >40 yr Schizophrenia Abdominal obesity/overweight Fatty liver First-degree relative with DM Hyperuricemia Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander) Hx of IGT or IFG HTN Dyslipidemia Medications e.g. 2nd generation antipsychotics PCOS Hx of gestational DM or macrosomic baby (>9 lb or 4 kg)
Body Habitus	Normal to thin	Typically overweight with increased central obesity
Treatment	Insulin	Lifestyle modification Non-insulin antihyperglycemic agents – unless contraindicated, metformin should be the initial antihyperglycemic agent of choice. Additional agents to be selected on the basis of clinically relevant issues, such as glucose lowering effectiveness, risk of hypoglycemia, and effect on body weight Insulin therapy
Acute Complication	Diabetic ketoacidosis (DKA) in severe cases	Hyperosmolar hyperglycemic state (HHS) DKA in severe cases
Screening	Subclinical proteome can be detected in first and second-degree relatives of those with type 1 DM by the presence of pancreatic islet autoantibodies	Screen individuals with risk factors

Summary

	Type 1 DM	Type 2 DM
Pathogenesis	• Autoimmune destruction of pancreatic Beta cells in genetically susceptible individuals and triggered by some environmental factors. • Characterized by a severe deficiency of insulin. • Not related to obesity	• Characterized by resistance to the action of insulin and an inability to produce sufficient insulin to overcome this 'insulin resistance'. • Obesity play a major role
Risk factors	• Factors that act as a trigger for the autoimmune response. • E.g infection with mumps virus, coxsackie B virus Rotavirus or EBV. • **HLA- DR3-DQ2, HLA- DR4-DQ8 genes or both**	• obesity • Sedentary lifestyle • PCOS • Metabolic syndrome • Impaired glucose tolerance • Impaired fasting glucose
Clinical presentation	polyuria Polydipsia Weight loss Blurred vision Fungal infections frequent urination Numbness, tingling of hands and feet	
Diagnosis	1. fasting plasma glucose (FPG) (Specific) 2. random glucose (Sensitive) 3. 2-hour plasma glucose after a 75- g oral glucose tolerance test (OGTT) (Sensitive & Specific) 4. The use of glycated haemoglobin (HbA1c) 5. Glycosuria	Table 2 – American Diabetes Association diagnostic criteria for diabetes[18] Test[a] / Threshold / Qualifier Hemoglobin A_{1c} or — ≥ 6.5% — Lab NGSP-certified, standardized DCCT assay Fasting glucose or — ≥ 126 mg/dL (7.0 mmol/L) — No caloric intake for at least 8 hours 2-hour glucose or — ≥ 200 mg/dL (11.1 mmol/L) — After 75 g of anhydrous glucose Random glucose — ≥ 200 mg/dL (11.1 mmol/L) — Plus classic hyperglycemia symptoms or crisis NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial. [a] Results must be confirmed by repeated testing.
Management	• Bolus (preprandial or mealtime) insulins : rapid acting and short acting insulin • Basal insulin : intermediate and long acting insulin • Premixed insulin • **MDI = Multiple Daily Injections (3 – 6 injections / day) is the preferred regimen for adults**	• Diet and lifestyle changes • The three main options are metformin, a sulfonylurea or a thiazolidinedione. • If control is inadequate on oral therapy, insulin therapy should be started without undue delay

Lecture Quiz

Q1: A 29-year-old man presents to his GP complaining of being constantly thirsty, tired and visiting the toilet more often than usual during the last 4 days. He has noticed his clothes have become more baggy and he now needs to tighten his belt. His parents both have diabetes requiring insulin therapy. A fasting plasma glucose result is most likely to be:

A. 9.0 mmol/L
B. 6.0 mmol/L
C. 16.3 mmol/L
D. 5.0 mmol/L
E. 3.0 mmol/L

Q2: A 41-year-old man has been recently diagnosed with type 2 diabetes and has been following a plan of lifestyle measures to improve his diet and increase his level of exercise. On returning to clinic, his BMI is 23, fasting plasma glucose 9.0 mmol/L, blood pressure 133/84 mmHg and HbA1c of 7.1 per cent. The most appropriate treatment option is:

A. Metformin
B. Sulphonylurea
C. Insulin
D. Exenatide
E. Further diet and exercise

Q3: Risk factors for T2DM include all of the following except :

A- Advanced age
B- obesity
C- Smoking
D- physical inactivity

Q4: Which of the following diabetic drugs acts by decreasing the amount of glucose produced by the liver ?

A- Sulfonylureas
B- Meglitinides
C- Biguanides
D- alpha glucosidase Inhibitor

Q5: A 47-year-old woman complains of weight loss. She has a family history of type 1 and type 2 diabetes but has never been diagnosed herself despite the finding of islet cell antibodies. In the last few months, however, she has noticed progressively increasing polyuria and polydipsia and 5 kg of weight loss. Her fasting plasma glucose is 8 mmol/L and urine dipstick shows the presence of ketones. The most likely diagnosis is:

A. Type 1 diabetes
B. Non-ketotic hyperosmolar state
C. Type 2 diabetes
D. Occult malignancy
E. Latent autoimmune diabetes of adults (LADA)

Q6 : **Which of the following regimens offers the best blood glucose control for persons with type 1 diabetes?**

A- A single anti-diabetes drugs
B- Once daily insulin injections
C- A combination of oral anti-diabetic medications
D- Three or four injections per day of different types of insulin.

Answers: Q1: A | Q2:B| Q3:C | Q4: C | Q5:E | Q6:D

GOOD LUCK !

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