ENDOCRINE SYSTEM

PBL

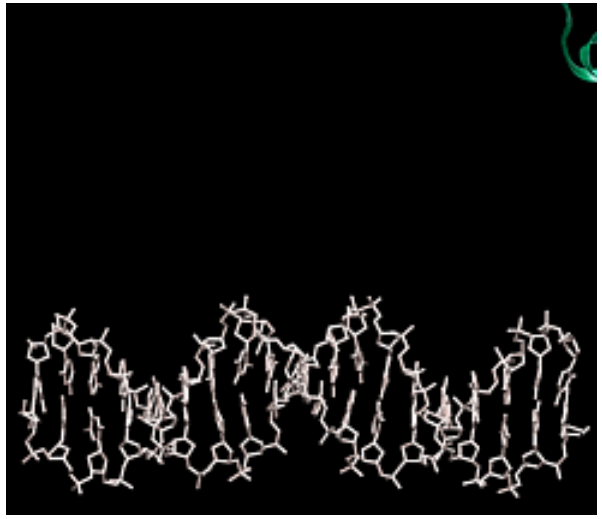
Lec. 1

WRITER: Ibrahem Al-Shawabkeh and Leen Abd

CORRECTOR: Hala Mousa

DOCTOR: Hiba Abbasi

ما ينطق به الدكتور من شرح سيكون باللون الأزرق
وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
ما يكون مهم في السلايدات يكون بخطين أو بخط



Hiba Abbasi,
MD,Endocrinologist
Department of Internal Medicine
School of Medicine
University of Jordan

Questions will come from discussed slides only.
What the doctor has read from the slides is underlined.
Let's get down to it!💪🔥

بسم الله الرحمن الرحيم

Diabetes mellitus

The History of Diabetes mellitus

- Approximately 1550BC an Egyptian manuscript mentions a rare disease that causes the patient to lose weight rapidly and **urinate frequently.** This is thought to be the first reference to diabetes.
- Around the 11 th Century, Some physicians taste the urine, and diabetes is given its second name mellitus, meaning '**sweet as honey'** in Latin.
- Diabetes mellitus is taken from the Greek word *diabetes*, meaning siphon - to pass through and the Latin word *mellitus* meaning sweet.

- In 1922 Banting, Best, and Collip purified the hormone insulin from the pancreas of cows at the University of Toronto, leading to the availability of an effective treatment for diabetes in 1922.
- Over the years, exceptional work has taken place, and multiple discoveries, as well as management strategies, have been created to tackle this growing problem.
- Unfortunately, even today, diabetes is one of the most common chronic diseases in the country and worldwide.

PREVALENCE

- Diabetes is estimated to affect > 500 millions adults worldwide, with a global prevalence of 10.5% among adults.
- Type 2 diabetes accounts for 90-95% of cases of diabetes worldwide. more common than type 1.
- The prevalence of type 2 diabetes has risen alarmingly in the past decade,linked to the trends in obesity and sedentary lifestyle.
- Given the marked increase in childhood obesity, there is concern that the prevalence of diabetes will continue to increase substantially.
- Type 1 diabetes accounts for another 5 to 10% of the cases.
- Known monogenic causes of diabetes represent a small fraction of cases (rare).

- Prevalence in Jordan is similar to the global prevalence ~ 11%

Classification of Diabetes Mellitus by Etiology

- **Type 1** is classified into subtypes according to the cause of the destruction of pancreatic beta cells (insulin secreting cells), although the treatment is the same for both subtypes :
- autoimmune destruction of the beta cells (type 1A)

  nonautoimmune islet destruction (type 1B)

What's a clinical evidence of the presence of an autoimmune destruction?
A Positive antibody titer which is detected in type 1A. This differentiates between the two subtypes of type 1 diabetes.
And a Negative antibody titer which indicates type 1B which may be due to a nonautoimmune cause like viral and environmental triggers.
*What are these antibodies directed against?
*Antigens known as islet cells components that could be any component of beta cells.

A student asked: Does the titer for type 1A have always to be positive?
*No, along time, the titer decreases, so at the onset of type 1A, the titer is much higher than about 10 years after (may be negative!!). So the classification of type 1 according to the antibody titer is relied on at the onset of the disease.

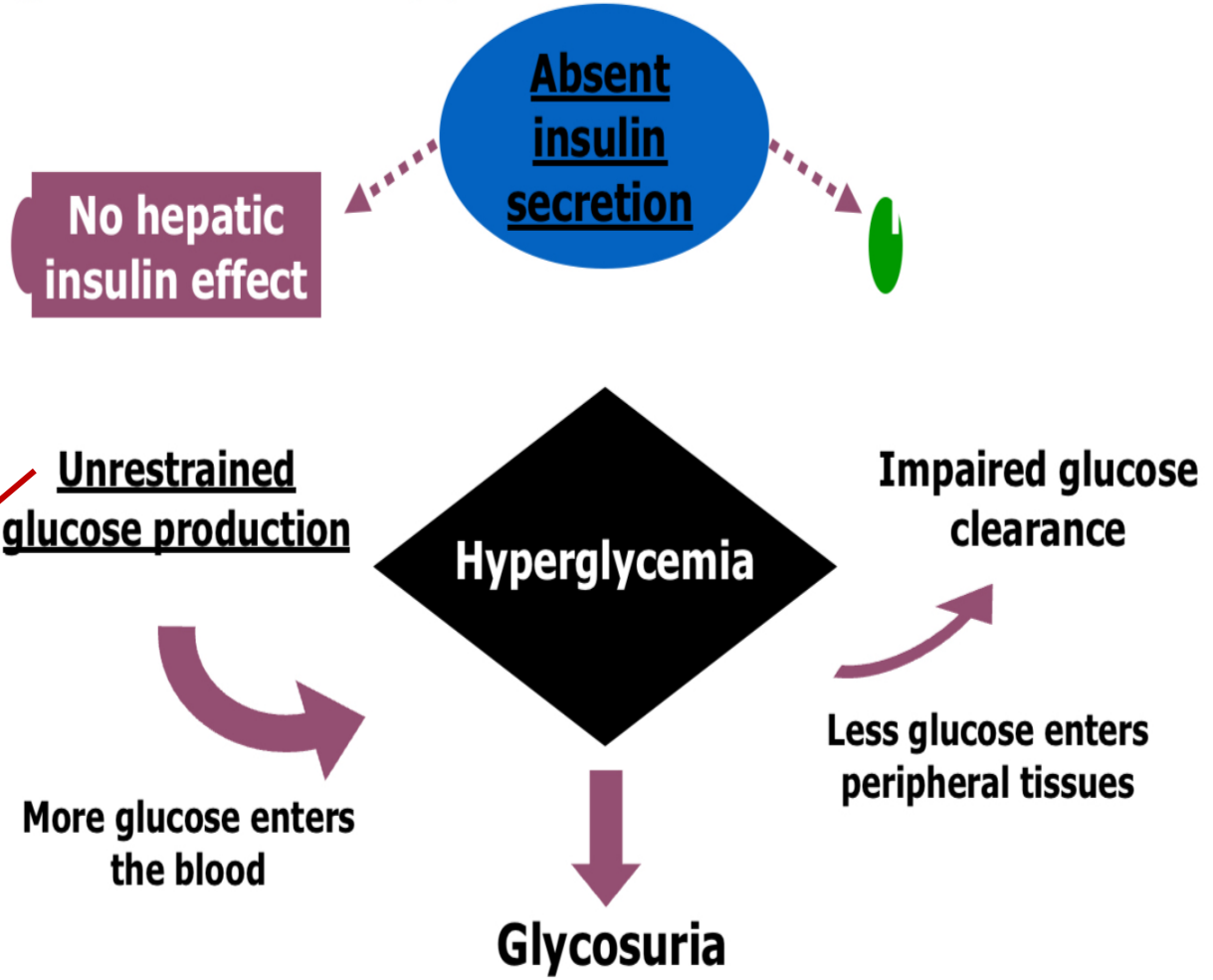
- **Type 2** β-cell dysfunction and insulin resistance. **A combination of relative insulin deficiency with relative insulin resistance.**

- **Gestational** β-cell dysfunction and insulin resistance **and the development of hyperglycemia during the second half of pregnancy . Pregnancy is known to be a physiological state of insulin resistance as placental hormones are diabetogenic which counteract the actions of insulin. Some ladies already have a predisposition to diabetes thus when becoming pregnant, diabetes can be triggered by the pregnancy.**

- **Other specific types** (secondary diabetes)
- Pancreatic diabetes.
- Endocrinopathies (the most common among less specific types)
- Drug- or chemical-induced
- Other rare forms

Pathogenesis of Type 1 Diabetes : One Defect

Pay attention, a possible exam question !!
Complete absence or lack of insulin = type 1 diabetes..
While in type 2= relative insulin deficiency



The most important action of insulin is applied on the liver (which is the inhibition of hepatic gluconeogenesis). When insulin is absent, it leads to unrestrained (excessive) glucose production

Type 1A diabetes:

- Autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans leading to absolute insulin deficiency.

- Occurs in **genetically susceptible** subjects, triggered by one or more **environmental agents**, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic.

- **Genetic susceptibility** :Polymorphisms of multiple genes are known to influence the risk of type 1A diabetes.
- **Target autoantigens** : There are a number of autoantigens within the pancreatic beta cells (**any component of beta cells including: insulin or its receptor, or the enzymes involved in glucose homeostasis starting with glucose sensors and ending with insulin secretors)**play important roles in the initiation or progression of autoimmune islet injury including:(**the most important among them are**): anti-glutamic acid decarboxylase (GAD), anti-GAD antibodies, anti-insulin antibodies, insulinoma-associated protein 2 (IA-2) and zinc transporter ZnT8.
- **Environmental factors** include pregnancy-related and perinatal influences, viruses, and ingestion of cow's milk and cereals.

Just memorize the most commonly detected which are :anti-GAD antibodies and anti-insulin antibodies:)

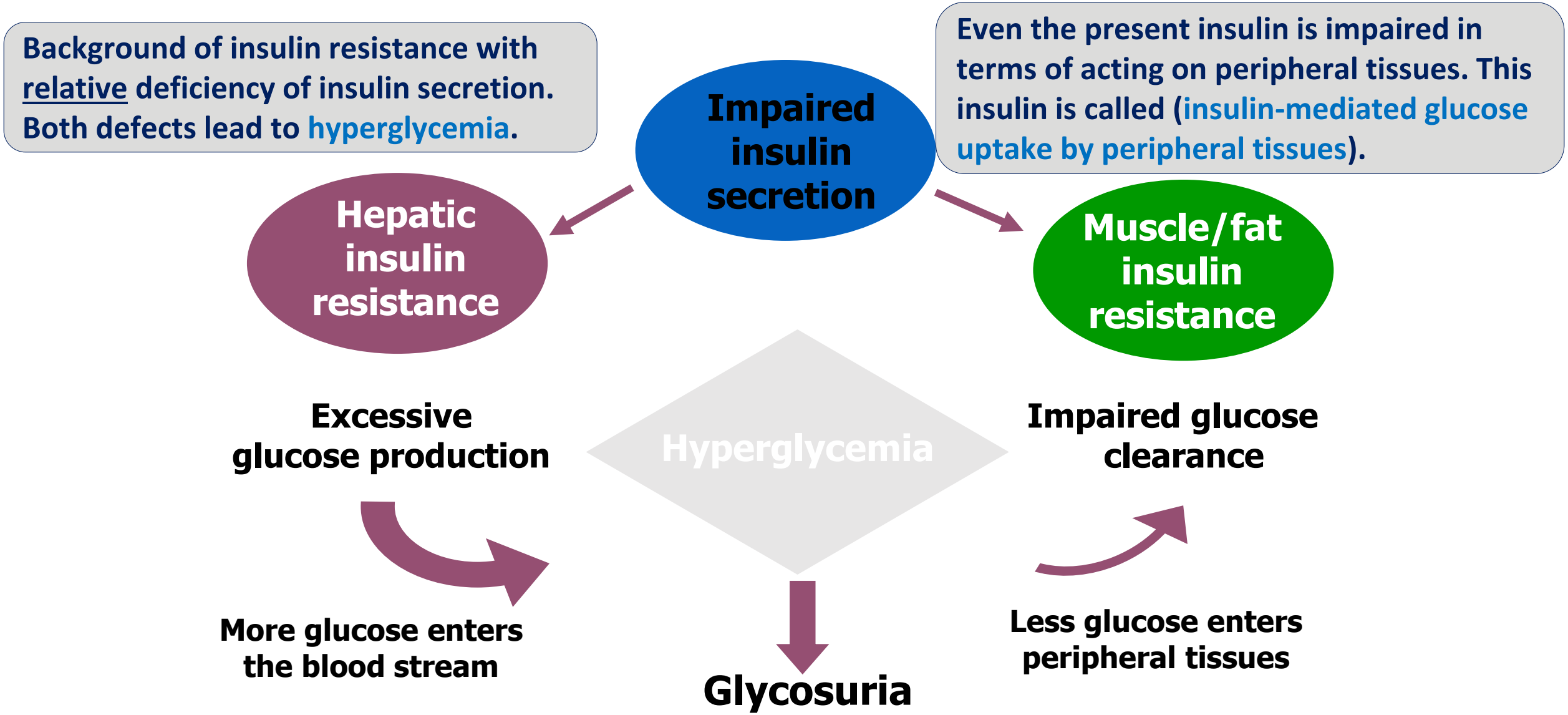
Confirmed targets of autoantibodies in type 1 diabetes

Insulin
Glutamic acid decarboxylase
Insulinoma associated antigens 2 (alpha and beta)
ZnT8 (zinc transporter)

Type 1B or "idiopathic" diabetes:

- Some patients with absolute insulin deficiency have no evidence of autoimmunity and have no other known cause for beta cell destruction. **There are ongoing studies looking for the pathophysiology leading to the complete lack of insulin along with the absence of antibodies.**
- Presence of nonautoimmune pathophysiologic processes leading to near-complete loss of beta cell function.

Pathogenesis of Type 2 Diabetes : Two Defects



Pathogenesis of type 2 diabetes mellitus

- Multifactorial

- Type 2 diabetes is a polygenic disease **(no certain gene is involved, opposite to the monogenic diabetes which will be discussed** 

), with complex interaction between genetic and environmental factors contributing to disease risk.

- Patients typically present with a combination of varying degrees of insulin resistance and defective insulin secretion (beta cell dysfunction).

- **Insulin resistance :**

Attributed to predominantly "environmental" factors **(more important than genetic factors!)** related to overeating, sedentary lifestyle, and resulting overweight and obesity(**reversing these factors will decrease the incidence of type 2 DM and even the remission of it)**with less prominent contributions from aging and genetics.

- **Impaired insulin secretion:**

Resulting from genetic influences and the programming of the beta cell mass and function in utero.

- Hyperglycemia itself can impair pancreatic beta cell function and exacerbate insulin resistance ("glucotoxicity"), leading to a vicious cycle of hyperglycemia causing a worsening metabolic state.

Monogenic diabetes (formerly called maturity onset diabetes of the young) formerly named: ‘Mody’’

**A Very rare type of diabetes and it’s a separate type!

Monogenic, so genetic tests can be performed to detect the gene defect that is responsible for diabetes.

- Diabetes diagnosed at a young age (<25 years)
- Autosomal dominant transmission and lack of autoantibodies.
- MODY is the most common form of monogenic diabetes, accounting for 2 to 5% of diabetes.
- Many patients are misclassified as having either type 1 or 2 diabetes.
- The original MODY nomenclature ("MODY1," "MODY2," "MODY3," etc) has been replaced by the term "monogenic diabetes" with the name of the gene associated with the trait.

- The involved genes control pancreatic beta cell development, function, and regulation. And the mutations in these genes cause **impaired glucose sensing and insulin secretion with minimal or no defect in insulin action.**
- Mutations in hepatocyte nuclear factor-1-alpha (*HNF1A,50-65%*) and the glucokinase

(*GCK,15-30%*) genes are the most commonly identified.

We need to conduct a genetic test for 3 or 4 generations to confirm that it's MODY.
Btw the test is not available in Jordan yet :)
Make a revolution and bring it!!

Latent autoimmune diabetes in adults (LADA) or Late onset diabetes of adults

Previously considered as a speech type but recently, it's been classified as a subtype of type 1 DM since its pathophysiology is an autoimmune destruction of beta cells. And the major difference between LADA and other subtypes of DM type 1 is the affected age group.

- **Diagnosis** :
- An adult-onset (above 40 yrs) diabetes who are positive for at least one islet autoantibody with prolonged preservation of insulin secretion.
- LADA may be considered a slowly progressive variant of type 1 diabetes. Patients with LADA are a heterogeneous group with variable titers of antibodies, body mass index (BMI), and rate of progression to insulin dependence.
- Adults with LADA may not require insulin treatment at diagnosis but typically progress to insulin dependence after several months to years.
- The presence and degree of elevation of anti-GAD or anti-ICA antibodies can help predict accelerated disease progression, an earlier requirement for insulin therapy, subtherapeutic (poor) responses to oral hypoglycemic medications, and greater risk of ketoacidosis.
- **Genetics**.In genotyping analyses, LADA shares genetic features of both type 1 and type 2 diabetes.

Gestational Diabetes

- Occurs when a woman's pancreatic function is insufficient to overcome the insulin resistance associated with the pregnancy state (placental secretion of diabetogenic hormones)
- Develops in the second or third trimester and usually resolves after birth.
- High risk of perinatal morbidity and mortality

Dr didn't explain this slide.

Gestational Diabetes

- High risk of later type 2 diabetes in both mother and baby.
- Diagnosed by specific glucose tolerance test methods.
- Requires intensive dietary and glycemic management.

Dr didn't explain this slide.

Clinical features distinguishing type 1 diabetes, type 2 diabetes, and monogenic diabetes*

Clinical features	Type 1 diabetes mellitus	Type 2 diabetes mellitus	Monogenic diabetes
Age of diagnosis (years)	Majority <25, but may occur at any age	Typically >25 but incidence is increasing in adolescents, paralleling increasing rates of obesity in children and adolescents¶	<25
Weight	Usually thin, but with obesity epidemic overweight and obesity at diagnosis becoming more common	>90% at least overweight	Similar to general population
Autoantibodies	Present	Absent	Absent
Insulin dependent	Yes	No	No
Insulin sensitivity	Normal when controlled	Decreased	Normal (may be decreased if obese)
Family history of diabetes	Infrequent (5 to 10%)	Frequent (75 to 90%)	Multigenerational, ie, ≥3 generations
Risk of diabetic ketoacidosis	High	Low	Low

You can skip the monogenic features!

The doctor stated that the previous table is very important for clinical purposes!

The patient's profile (his name/age/work/address/weight/marital status.. Etc) is helpful for the diagnosis of diabetes , if it's either type 1 or 2..

*Guess.. Could a patient with type 1 diabetes have signs of insulin resistance?

It's supposed to be no, since there's a no relation between them. But in case of obese patients, you may become confused about the type of DM, since **most DM type 2 patients are obese**, but some children (especially in communities with a high prevalence of obesity) may also have DM type 1, but **the obesity is absolutely not the cause of DM type 1** and have no influence on the development of type 1 as it was assigned for those children to have DM type 1 since being in-utero because it's related to their **GENETICS** 🧬. So obesity and DM type 1 can only **COEXIST** together and…

⚜**THE PRESENCE OF OVERWEIGHT OR OBESITY DOESN'T EXCLUDE AND DOESN'T CONTRADICT THE POSSIBILITY OF TYPE 1 DIABETES IN THE PATIENT**⚜

Major Risk Factors (Type2 DM)

Check the next slide first!

Categories of increased risk for diabetes (prediabetes)*

FPG 100 to 125 mg/dL (5.6 to 6.9 mmol/L) – IFG
2-hour post-load glucose on the 75 g OGTT 140 to 199 mg/dL (7.8 to 11.0 mmol/L) – IGT
A1C 5.7 to 6.4% (39 to 46 mmol/mol)

Prediabetes "مرحلة ما قبل السكري" is the most important risk factor of diabetes.
The previous table is important !

There are three diagnostic criteria to diagnose DM:

1)**Fasting plasma glucose (FPG)**: the level of plasma glucose after fasting (zero calories intake) for at least 8 hours.
100=< FPG =< 125 mg/dL 👉 prediabetes
FPG >= 126 mg/dL 👉 Diabetes

2) 2-**hours post-load glucose**: administration of 75g of glucose orally then measuring the glucose level.
140=< post glucose load =< 199 mg/dL 👉 impaired glucose tolerance
Post glucose load >= 200 mg/dL 👉 Diabetes
-impaired glucose tolerance means that the body can't regulate glucose level so it is prediabetes

3) **A1C test** 'السكر التراكمي':measures the average of hemoglobin attached to glucose (glycosylated hemoglobin) over the past 3 months.
*For 3 months because RBC's lifespan is about 120 days.
- **5.7=< A1C =< 6.4% 👉 prediabetes**
- **A1C >= 6.5% 👉 diabetes**

- **DM is a progressive disease** (**progressive destruction of beta cells**) so it is very unlikely for prediabetic patients to remain prediabetic without developing diabetes, they commonly become diabetic but when? Nobody knows!
- Less than 20% of prediabetic patients won't progress to DM.
- As we said earlier, **environmental factors are the major risk factor** (mainly **obesity** and **inulin resistance**) for DM, so if these factors are reversed, the progression and incidence of DM is reduced.
- There is a big difference between DM remission and cure.
- **Remission** means there is a **chance of relapse (euglycemic 'normal glucose levels ')** while **Cure** means the patient is **completely healed.**

- **A diabetic patient cannot be cured from diabetes, in best circumstances, we say that the diabetes is controlled and once environmental factors are negatively reversed, diabetes will be back!**😈

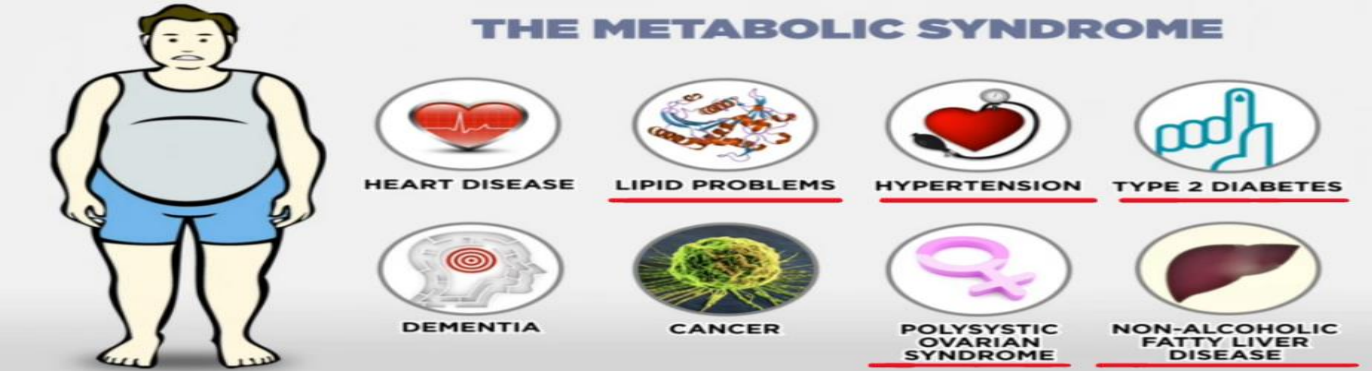
Medical conditions associated with an increased risk of **type 2 diabetes** including:

Risk factors:

1. Gestational diabetes (any lady that suffers from gestational diabetes during pregnancy is at higher risk of developing DM type 2)

2. Polycystic ovary syndrome (a metabolic condition with a high risk of type 2 DM)

- Metabolic syndrome "syndrome X" that's associated with hypertension, hyperglycemia, dyslipidemia, diabetes and obesity (measured by the waist circumference).
- Another example is Non-Alcoholic Steatohepatitis 'NASH'



Obesity

- Obesity is the most important modifiable risk factor for type 2 diabetes.
- Inducing resistance to insulin-mediated peripheral glucose uptake.
- The mechanism by which obesity induces insulin resistance is poorly understood.
- Reversal of obesity decreases the risk of developing type 2 diabetes and improves glycemic management and can lead to **remission** in diabetic patients.

- The degree of insulin resistance and the incidence of type 2 diabetes are highest in those with central or abdominal obesity, as measured by waist circumference.

- Intra-abdominal (visceral) fat rather than subcutaneous or retroperitoneal fat appears to be of primary importance.

- Why the pattern of fat distribution is important and the relative roles of genetic and environmental factors in its development are not known!

Family history/Genetic susceptibility

Despite that DM1 is attributed to genetic factors, family history in DM2 is much more important!

- The risk is likely mediated through genetic, anthropometric (BMI and waist circumference), and lifestyle (diet, physical activity, smoking) factors.
- Any first degree relative ….. 2X-3X increase risk of developing DM.
- With both a maternal and paternal history of type 2 diabetes…5X-6X increase risk of DM .
- Insulin resistance and impaired insulin secretion in type 2 diabetes have a substantial genetic component.

Lifestyle factors

- Insulin resistance and impaired insulin secretion can be influenced, both positively and negatively, by behavioral factors, such as physical activity, diet, smoking, alcohol consumption, body weight, and sleep duration. Improving these lifestyle factors can reduce the risk of diabetes mellitus.

Lifestyle modification is the reversal of environmental factors such as physical activities, diet restriction, quitting smoking, quitting alcohol consumption, regulating sleep patterns and weight reduction. All can reduce the risk of DM type 2.

Exercise

Exercise has a direct positive effect on glucose levels even if it doesn't lead to weight reduction. It enhances insulin resistance and sensitivity regardless of the weight reduction!

- A sedentary lifestyle lowers energy expenditure, promotes weight gain, and increases the risk of type 2 diabetes .
- Among sedentary behaviors, prolonged television watching is consistently associated with the development of obesity and diabetes.
- Physical inactivity, even without weight gain, appears to increase the risk of type 2 diabetes.
- Physical activity of moderate intensity reduces the incidence of new cases of type 2 diabetes, regardless of the presence or absence of IGT.

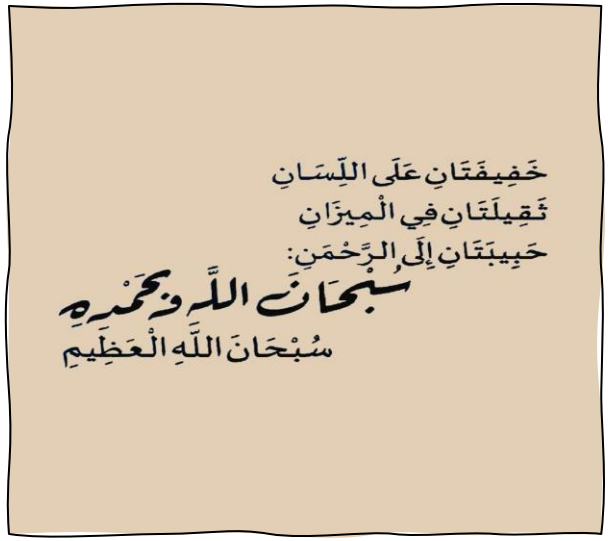
Smoking

- Several large prospective studies have raised the possibility that cigarette smoking increases the risk of type 2 diabetes.
- Secondhand smoke also increases the risk.
- While a definitive causal association has not been established, a relationship between cigarette smoking and diabetes mellitus is biologically possible based upon a number of observations:

1. Smoking increases the blood glucose concentration after an oral glucose challenge.
2. Smoking may impair insulin sensitivity.
3. Cigarette smoking has been linked to increased **abdominal** fat distribution (visceral or intra-abdominal obesity).

Dietary patterns

Adherence to a diet high in fruits, vegetables, nuts, whole grains, and olive oil is associated with a lower risk of type 2 diabetes.



CLINICAL PRESENTATION

Type 2 DM can be detected early throughout screening (annual routine checkups)

- The majority of patients are **asymptomatic** at presentation, with hyperglycemia noted on routine laboratory evaluation.
- The frequency of symptomatic diabetes has been decreasing in parallel with improved efforts of screening.
- The classic symptoms (**catabolic presentation**)of hyperglycemia (including polyuria, polydipsia, nocturia, blurred vision, and weight loss) are often noted only in retrospect after high blood glucose reading.
- DKA (**Diabetic ketoacidosis**)as the presenting symptom of type 2 diabetes is uncommon **(more common in type 1)** but may occur under certain circumstances (usually severe infection or other acute illness).
- Hyperosmolar hyperglycemic state(marked hyperglycemia, severe dehydration, and obtundation, but without ketoacidosis) is rare.

Type 1 DM

- DKA is the initial presentation in about 25% of adults with newly diagnosed type 1 diabetes.
- More common in children than in adults with type 1 DM

DKA is more common in DM1 due to the complete absence of insulin which is the most important factor in the development of DKA.

Have been discussed previously ⏮

American Diabetes Association criteria for the diagnosis of diabetes

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* **OR**
2. FPG ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.* **OR**
3. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* **OR**
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

This is the last required slide! 😅

Management of diabetes

1. Lifestyle modifications (**nonpharmacological management**):

- Medical nutrition therapy
- increased physical activity
- weight reduction

If nonpharmacological management fails ,we move to pharmacological therapy. Also, along with the pharmacological remedies, we don't abandon lifestyle modification! **So pharmacotherapy is 2nd to lifestyle modification**

2. Oral Drug Therapy/Noninsulin SC therapy (**non injectable medication**)
3. Insulin therapy (**injectable medication**)

TREATMENT GOALS

1- **Diabetes Education** : instruction on nutrition, physical activity, optimizing metabolic control, and preventing complications.

2- Evaluation for micro- and macrovascular complication

3- **Attempts to achieve near normoglycemia**

4- Minimization of cardiovascular and other long-term risk factors

5- Avoidance of drugs that can exacerbate abnormalities of insulin or lipid metabolism.

Dr didn't explain this slide.

Diabetes Education

Intensive lifestyle modification

Intensive behavioral modification interventions including weight reduction and increasing activity levels are successful in

- Reducing weight
- Improving glycemic management
- Reducing the need for glucose-lowering medications.

Dr didn't explain this slide.

1- Medical nutrition therapy

Aiming for weight reduction or at least weight maintenance.

2- Weight reduction

- By diet control, pharmacological or surgical therapy.

- Improved glycemic state is induced by weight loss through partial correction of the two major metabolic abnormalities in type 2 diabetes: insulin resistance and impaired insulin secretion.

- Weight loss and weight loss maintenance supports all effective type 2 diabetes therapy and reduces the risk of weight gain associated with sulfonylureas and insulin.

Dr didn't explain this slide.

3- Exercise

- Regular exercise is beneficial for diabetics independent of weight loss.

- It leads to improved glycemic management due to : increased responsiveness to insulin and so delay the progression of impaired glucose tolerance to overt diabetes.

- These beneficial effects are directly due to exercise.

- Unfortunately, in one study, only 50% of patients with type 2 diabetes were able to maintain a regular exercise regimen.

Dr didn't explain this slide.

و في ختام السّنة الثانيّة، نرجو من الله أن نكون وُفِّقنا في عملنا و رُزِقنا القَبول والأجرَ، فلا تنسونا و أهلَنا المستضعفين في مشارق الأرض و مغاربها من حسن دعائكم و إعدادكم أنفسكم لنصرتهم فكلّنا على ثغور،فلا يؤتين الإسلام من قِبلنا.

فنحن البناء لهذه الأمة، و من كان بناءً فعليه ألّا يستريح.

دمتم بحفظ الله و رعايته على أن نلقاكم في قادم الأعوام على خيرٍ إن شاء الله.

-فريق طوفان الأقصى.