بسم الله الرحمـٰن الرحيم

{وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ}

PBL Clinical | FINAL 1

Diabetes Mellitus

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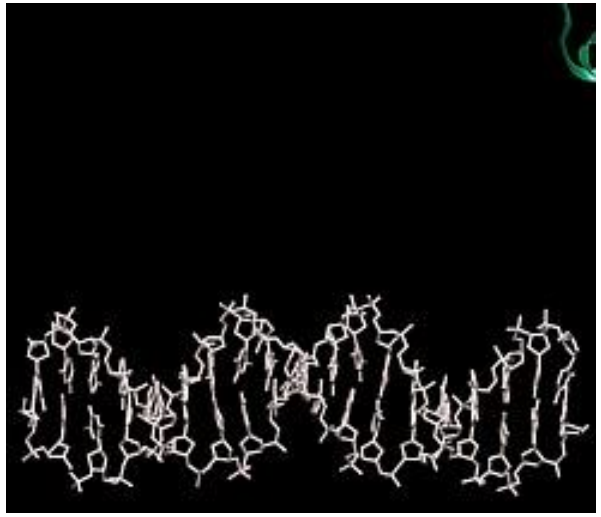

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Diabetes mellitus

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.
- 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.

Classification of Diabetes Mellitus by Etiology

- **Type 1** — autoimmune destruction of the beta cells (type 1A) / nonautoimmune islet destruction (type 1B)

It has subtypes likeLADA

- **Type 2** — β-cell dysfunction and insulin resistance
- **Gestational** — β-cell dysfunction and insulin resistance during pregnancy

- **Other specific types**
  - Pancreatic diabetes.
  - Endocrinopathies
  - Drug- or chemical-induced
  - Other rare forms

Classification of Diabetes Mellitus by Etiology

Diabetes mellitus can be classified into different types according to etiology. This means that the different types are classified based on differences in their pathogenesis, rather than differences in their clinical presentation or management.

Type 2 diabetes mellitus:

The pathogenesis of type 2 diabetes involves a combination of variable degrees of insulin resistance and impaired insulin secretion, with insulin resistance being the more common feature

- **Type 1**

There are two types:
Type 1A: Positive for autoimmune markers.
Type 1B: Negative for autoimmune markers.

Classification of Diabetes Mellitus by Etiology

There are different explanations or theories regarding type 1B diabetes.
The first explanation is related to the timing of antibody testing.
An autoantigen is an antigen that represents a component of the body's own tissues.
In diabetes, the antigen may be a component related to the pancreatic islet cells, such as the islet cells themselves, insulin receptors, insulin, or enzymes involved in glucose homeostasis.
At the very beginning of the disease, before the patient develops symptoms or hyperglycemia, autoimmune destruction is already ongoing. At this stage, the antibody titer is high because the antigen is still present and is being destroyed.
When destruction exceeds approximately 80%, hyperglycemia develops and the patient becomes symptomatic.
After extensive destruction has occurred, the antibody titer may decrease. Therefore, when the patient is eventually tested, the antibodies may be negative.
This provides one possible explanation for why a patient with type 1B diabetes may test negative for autoimmune markers despite a possible autoimmune process.
Another explanation currently being investigated is that type 1B diabetes may not involve autoimmune destruction at all, and that another underlying mechanism may be responsible.

Classification of Diabetes Mellitus by Etiology

3. Gestational Diabetes Mellitus (GDM)

The pathogenesis of gestational diabetes is related to the physiological state of insulin resistance that occurs during pregnancy due to pregnancy-related hormones.
However, not all pregnant women develop gestational diabetes. Whether a pregnant woman develops GDM depends on a combination of genetic and environmental factors.

4. Pancreatic Diabetes

Diabetes is considered pancreatic diabetes when it develops as a result of a structural disease of the pancreas.
Examples include:
Chronic pancreatitis
Pancreatic malignancy
Cystic fibrosis
In cystic fibrosis-related diabetes, the treatment and complications are similar to those of type 1 diabetes.

Classification of Diabetes Mellitus by Etiology

5. Secondary Diabetes Due to Endocrine Pathology

Diabetes can also occur secondary to endocrine disorders. Most of these endocrine conditions cause diabetes by increasing insulin resistance.

Examples include conditions associated with excess hormones:

- Excess cortisol(Cushing syndrome)—-Adrenal causes or Pituitary causes, such as Cushing disease
- Excess growth hormon(Acromegaly)

In these cases, diabetes develops secondary to the underlying endocrine disorder and is therefore referred to as secondary diabetes.

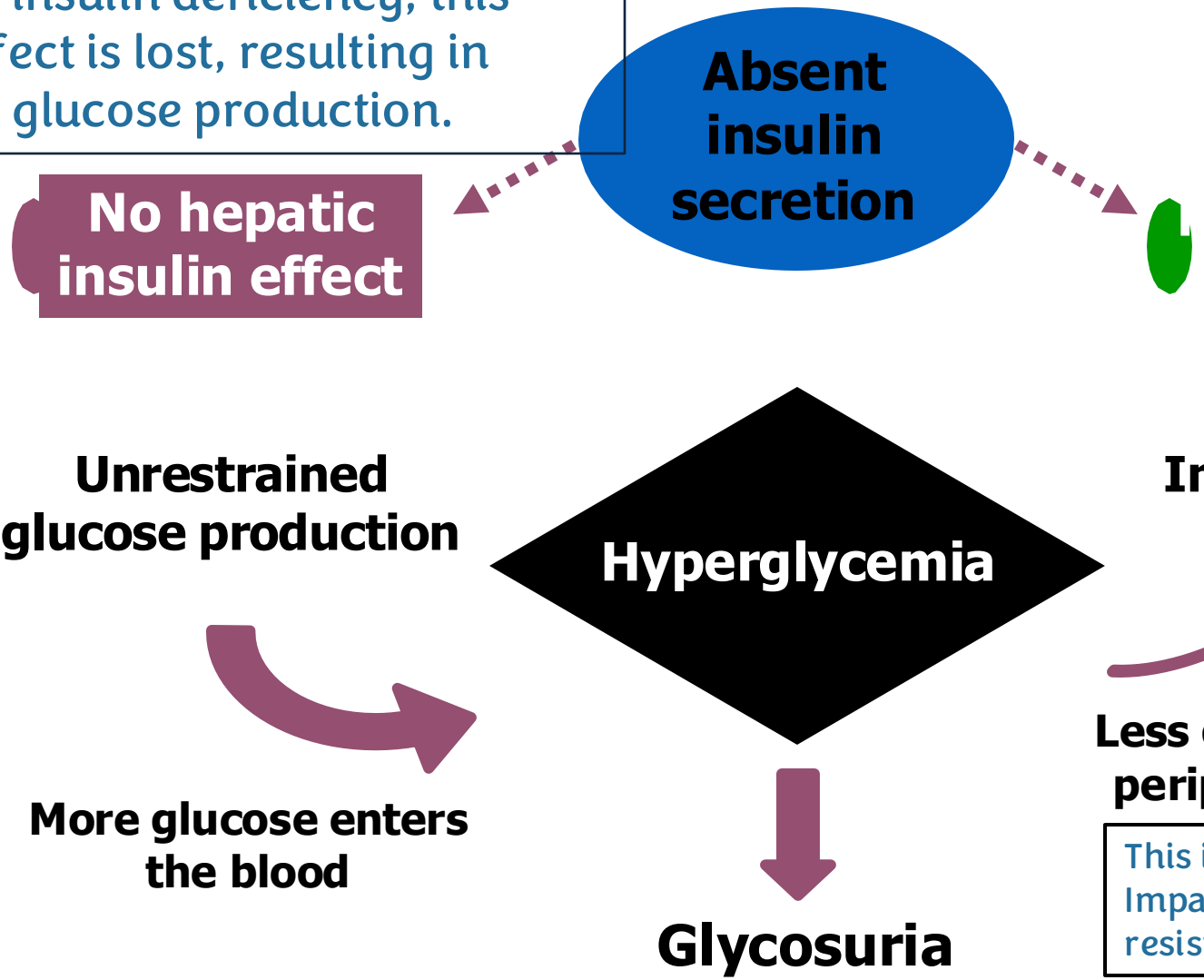
6.Drug-Induced Diabetes

Another type is drug-induced diabetes.

An example is diabetes induced by glucocorticoids, also known as steroid-induced diabetes.

Pathogenesis of Type 1 Diabetes : One Defect

1)One of the actions of insulin is the inhibition of gluconeogenesis. Therefore, in insulin deficiency, this inhibitory effect is lost, resulting in unrestrained glucose production.



2)insulin resistance is decreased glucose uptake by peripheral tissues, particularly skeletal muscle and adipose tissue.

This is the combination of:
Impaired insulin secretion + insulin resistance

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**,

  Why can Type 1 diabetes develop at different ages?
  Type 1 diabetes can present at different ages, for example at 8, 9, 23, or even 30 years of age.
  The timing of its development may be related to exposure to environmental triggers in a susceptible individual.

- and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. This long latent period is a reflection of the large number of functioning beta cells that must be lost before hyperglycemia occurs.

- **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 play important roles in the initiation or progression of autoimmune islet injury including: glutamic acid decarboxylase (GAD), insulin, 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.

Confirmed targets of autoantibodies in type 1 diabetes

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

Autoantibodies in Type 1 diabetes

When investigating autoimmune type 1 diabetes, testing for multiple types of autoantibodies increases the possibility of detecting autoimmune diabetes.

However:

Negative autoantibodies do NOT necessarily exclude autoimmune Type 1 diabetes.

Therefore, testing more than one type of antibody can be helpful when evaluating a patient suspected of having type 1 diabetes.

Differentiating Type 1 from Type 2 diabetes

When a patient is newly diagnosed with diabetes and wants to know whether they have type 1 or type 2 diabetes, it may be difficult to give a definitive answer at the first visit.

In some patients, it may take months before the clinical picture becomes clear enough to distinguish between the two.

Patients are often concerned about this distinction because they may hope that they will not require lifelong insulin therapy.

However, the old terminology:
Type 1 = insulin-dependent diabetes mellitus
Type 2 = non-insulin-dependent diabetes mellitus
is no longer considered accurate.
This is because patients with type 2 diabetes may also eventually require insulin therapy at a certain stage of their disease.
Therefore, while the exact type of diabetes is still being investigated, the physician should explain the situation to the patient and provide the appropriate treatment for their current condition.
The diagnostic approach may include:

- Testing different and multiple autoantibodies
- Considering the patient's age group
- Considering relevant environmental factors
- **Assessing the overall clinical picture**

If the overall clinical picture suggests type 1 diabetes but autoantibodies are not detected, the patient may have Type 1B diabetes.

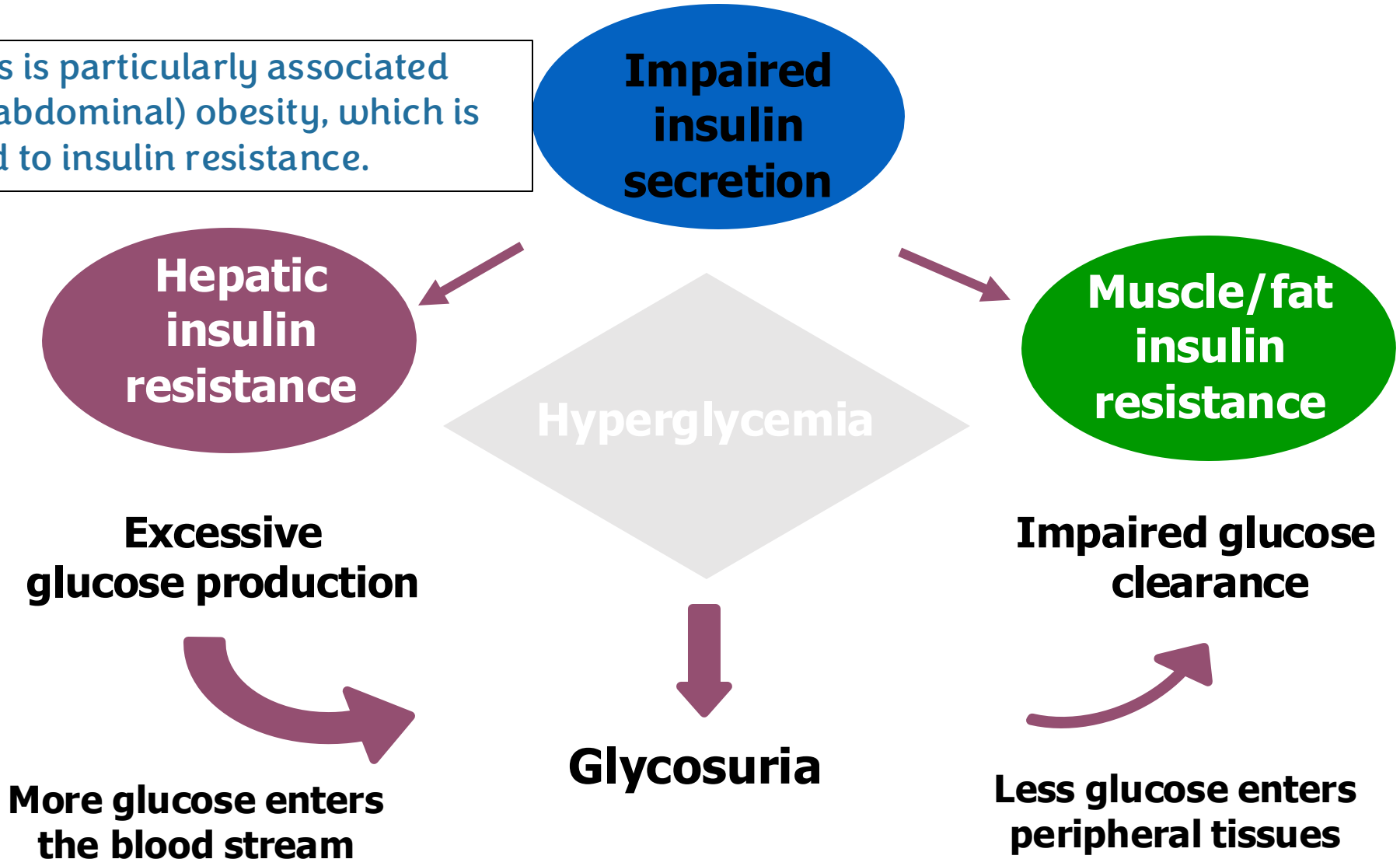
Type 1B or "idiopathic" diabetes:

- Some patients with absolute insulin deficiency have no evidence of autoimmunity and have no other known cause for beta cell destruction.

- Presence of nonautoimmune pathophysiologic processes leading to near-complete loss of beta cell function.

Pathogenesis of Type 2 Diabetes : Two Defects

Type 2 diabetes is particularly associated with visceral (abdominal) obesity, which is strongly linked to insulin resistance.



Pathogenesis of type 2 diabetes mellitus

- Multifactorial

- Type 2 diabetes is a polygenic disease, 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 :**

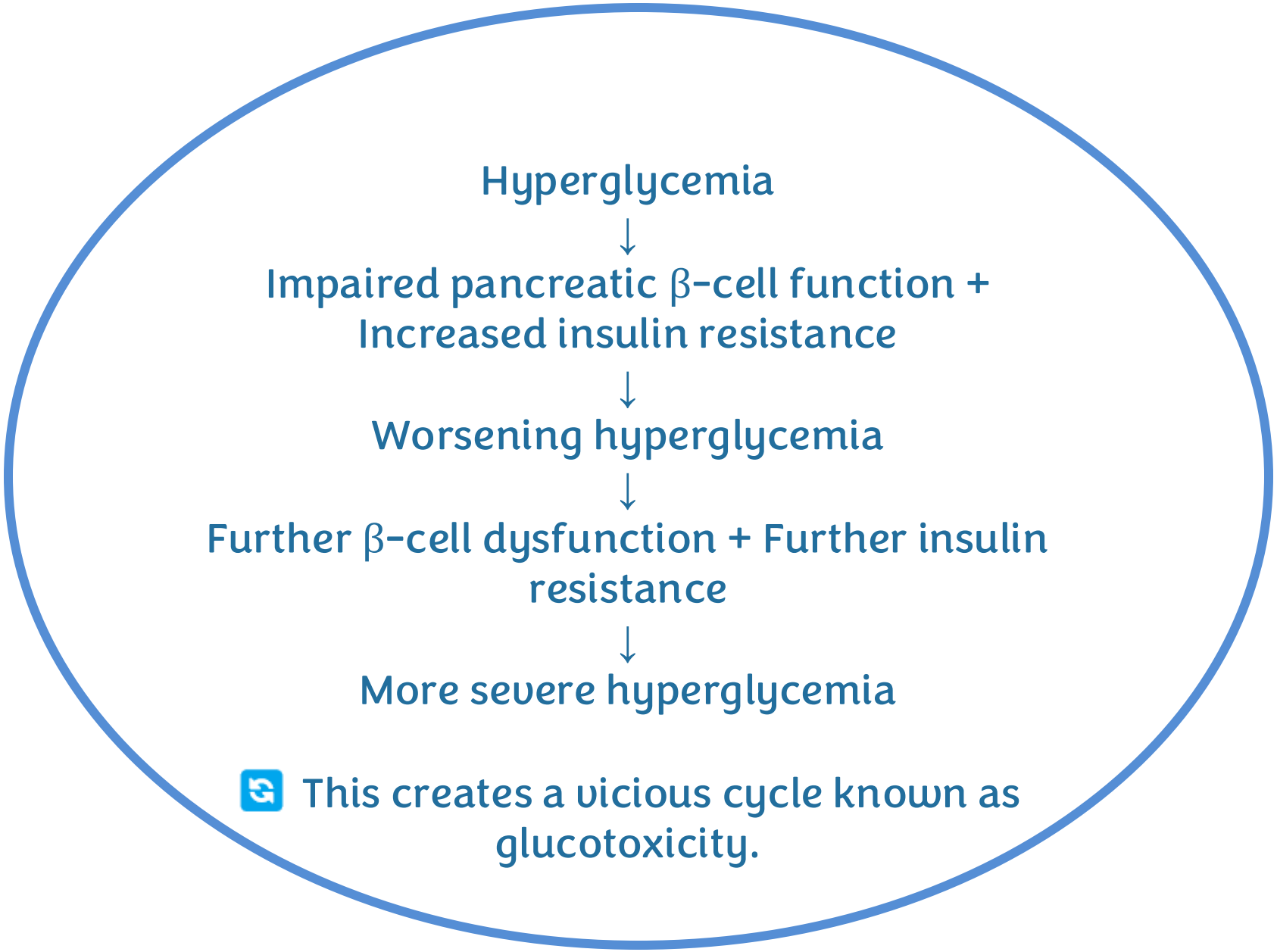
Attributed to predominantly "environmental" factors related to overeating, sedentary lifestyle, and resulting overweight and obesity, with less prominent contributions from aging and genetics.

- **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.

Vicious Cycle



Monogenic diabetes (formerly called maturity onset diabetes of the young)

- 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.
- Several different genetic abnormalities have been identified, each leading to a different type of disease.
- The original MODY nomenclature ("MODY1," "MODY2," "MODY3," etc) has bee replaced by the term "monogenic diabetes" with the name of the gene associated with the trait.

Monogenic Diabetes

Monogenic diabetes is a rare form of diabetes caused by a mutation in a single gene.
This differs from type 2 diabetes, which is multifactorial and results from the interaction of both genetic and environmental factors.
Traditionally, different forms of monogenic diabetes were classified as:
MODY 1, MODY 2, MODY 3, etc.
MODY = Maturity-Onset Diabetes of the Young
Nowadays, classification increasingly refers to the specific affected gene rather than relying only on the MODY number.

- The genes involved 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.

- Mutations in hepatocyte nuclear factor-4-alpha (*HNF4A*) account for approximately 10% of MODY cases.
- Some members of a family have the genetic defect but do not develop diabetes; the reason for this is unclear. Other patients may have the MODY phenotype but do not have an identifiable mutation in any of the known MODY genes.

Latent autoimmune diabetes in adults (LADA)

- **Diagnosis** :
- An adult-onset 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 clinical utility of the diagnosis lies in the identification of patients with a clinical course that will differ from that in patients with type 2 diabetes. 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 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.

LADA – Latent Autoimmune Diabetes in Adults

- LADA is considered a **slowly progressive** variant of Type 1 diabetes mellitus. It has characteristics that place it somewhat between Type 1 and Type 2 diabetes.
- The main features that vary among patients are:

1. Antibody titers
2. Degree of β-cell destruction
3. Rate of progression toward insulin dependency

LADA vs. Type 1 Diabetes

The most important distinction is the condition of the β-cells at the time of diagnosis.

Type 1 diabetes

At diagnosis:

There is usually **extensive/near-complete β-cell destruction.**

Therefore, there is severe or complete insulin deficiency.

Consequently, **symptoms** of hyperglycemia are generally **more prominent at presentation.**

LADA

At diagnosis:

β-cell destruction is **gradual** rather than rapid.

Therefore, there is still **residual β-cell function.**

Some endogenous insulin production remains.

Progression to complete β-cell destruction is therefore **slower than in Type 1 diabetes, but faster than in Type 2 diabetes.**

Important: The exact time required for LADA to progress to complete β-cell dysfunction is **unpredictable**. It may occur after:

3 months

1 year

3 years

Or even longer

Therefore, the rate of progression varies considerably between patients.

Age of Presentation

Age can help distinguish the different forms of diabetes:

Type 1 < LADA < Type 2

Type 1: generally presents at the youngest age.

LADA: typically presents in adulthood, with an average age around **35–45 years**.

Type 2: generally presents at an older age.

However, **age does not exclude LADA**. A patient in their **70s**, for example, can still present with LADA.

If LADA is diagnosed and the patient has significant β-cell dysfunction, **insulin therapy may be required from the time of diagnosis**.

In contrast, in typical **Type 2 diabetes**, initial treatment commonly involves **oral glucose-lowering therapy**, with **metformin** being a common first-line option.

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.(if before that is could be undiagnosed type 2)
- High risk of perinatal morbidity and mortality

Gestational Diabetes Mellitus

Gestational diabetes is diabetes that develops or is first recognized **during pregnancy**.

Its development is influenced by both:

- **Genetic factors**
- **Environmental/metabolic factors**

Example: BMI and Risk

Consider two pregnant women:

Woman A: **BMI = 35**

Woman B: **BMI = 25**

Woman A has a **higher risk of developing gestational diabetes**, because higher body weight/obesity is an important risk factor.

Family History

A **family history of Type 2 diabetes** also increases the risk of gestational diabetes.

For example:

If a woman's mother has Type 2 diabetes, that woman has a higher risk of developing gestational diabetes.

Future Risk

Gestational diabetes is also important because the mother has a **substantial increased risk of developing Type 2 diabetes later in life(>50%)**.

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.

Gestational Diabetes Mellitus

Gestational diabetes affects both the **mother and the fetus**. It could cause **deformities in the fetus** or increase **amniotic fluid**, causing problems during labor. It also increases the risk of developing **gestational diabetes in other pregnancies**.

Management

It requires **dietary lifestyle management** and/or **medical management**, either **oral medication or insulin**.

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

Regarding the previous table

Distinguishing Type 1, Type 2, and MODY:
When comparing **Type 1 diabetes, Type 2 diabetes, and MODY**, focus particularly on the stars above.

- **Family History**

Family history is relevant to both Type 1 and Type 2 diabetes, but it is **particularly important in Type 2 diabetes**.
Do not make the mistake of thinking:
"Because Type 1 diabetes has an important genetic component, family history must therefore be more important in Type 1 than Type 2."
Instead, remember that **Type 2 diabetes has a particularly strong familial/genetic predisposition**.
For example:
Having **one sibling with Type 1 diabetes** does not mean the risk is greater than having **multiple family members with Type 2 diabetes**.
(It's the other way around)
Multiple affected family members with Type 2 diabetes strongly suggest a familial predisposition.

Risk of Diabetic Ketoacidosis (DKA)
The risk of **DKA is higher in Type 1 diabetes**.
Why?
Because in Type 1 diabetes there is **severe or absolute insulin deficiency**.
Without sufficient insulin:
↓ Insulin → ↑ Lipolysis → ↑ Free fatty acids → ↑ Ketone bodies → DKA
Therefore, Type 1 diabetes has a much stronger association with DKA than typical Type 2 diabetes.

Major Risk Factors (Type2 DM)

- There are three important laboratory approaches discussed here.
- The numerical cutoffs are very important to memorize.

Categories of increased risk for diabetes (prediabetes)*

approximately 25% of people in Jordan are diabetic or prediabetic.

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)

Fasting Plasma Glucose (FPG)
Fasting means the patient has had no caloric intake for approximately 8 hours.
- Normal

< 100 mg/dL
- Prediabetes – Impaired Fasting Glucose (IFG)

100–125 mg/dL
- Diabetes

≥ 126 mg/dL

Important point about fasting duration
The intended fasting period is approximately 8 hours.
Do not intentionally extend fasting unnecessarily—for example, coming to the clinic after fasting for 14 hours. (it might be inversely related with accuracy)

Oral Glucose Tolerance Test (OGTT)
In the oral glucose tolerance test, we want to see how the body handles a known amount of glucose. So, we give the patient **75 g of glucose orally**, then wait for 2 hours and measure the blood glucose level. If the glucose is **less than 140 mg/dL,** it is normal; if it is **140–199 mg/dL**, this indicates **impaired glucose tolerance** (prediabetes); and if it is **≥200 mg/dL,** it indicates diabetes.
The important thing is not to confuse the **OGTT with random glucose**. In an OGTT, we are the ones giving the patient 75 g of glucose, so everyone receives the same glucose load and we see how their body responds to it after 2 hours. In contrast, with a random glucose measurement, the patient simply comes to the clinic at any time, maybe after eating a meal 2–3 hours ago, and we measure their glucose as it is. We don't give them a specific amount of glucose. So, if a patient eats a normal meal and comes 2 hours later for a glucose measurement, that is random glucose, not an OGTT.

Glycated Hemoglobin (HbA1c) (السكر التراكمي)
HbA1c can also be used for diagnosing diabetes.
Diabetes
HbA1c ≥ 6.5%
The key value to memorize is:
6.5% → Diabetes

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

1. Gestational diabetes
2. Polycystic ovary syndrome
3. Metabolic syndrome

Certain conditions are strongly associated with increased insulin resistance. One important example is polycystic ovary syndrome (**PCOS**), in which insulin resistance is commonly present and can contribute to the metabolic abnormalities associated with the condition.

Another major association is **metabolic syndrome (like metabolic liver disease),** which is characterized by a cluster of metabolic abnormalities, including steatohepatitis, hypertension, dyslipidemia, and increased abdominal (central) obesity. These abnormalities are closely associated with increased insulin resistance.

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. **(Very important)**

Obesity is one of the most important **risk factors for Type 2 diabetes** and is considered the most important **modifiable** risk factor. If obesity is the only risk factor in a patient, then **losing weight** through dietary modification and lifestyle changes can significantly **reduce the risk of developing** Type 2 diabetes. Moreover, if the patient is already in the **early stages** of the disease, substantial weight loss may improve insulin sensitivity and glucose control to the point that the diabetes can go into **remission**.

- 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** **(because it substantially increases insulin resistance)**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!

Males are more likely to develop fat deposition in the **abdomen**, giving them an **apple-shaped** pattern of fat distribution,

whereas **females** are more likely to accumulate fat around the **hips** and thighs, giving them a **pear-shaped** pattern

Family history/Genetic susceptibility

- 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 in type 2 diabetes have a substantial genetic component, and 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.

Exercise

- 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.

Regarding exercise and physical activity, **physical inactivity** increases the risk of developing type 2 diabetes **even** if it is **not** associated with **weight gain**. Therefore, we should encourage patients, and people in general—especially the older population—to remain physically active every day, regardless of whether they lose weight in this process or not , because regular physical activity provides metabolic benefits and helps reduce the risk of type 2 diabetes independently of weight loss.
So even inactivity increases insulin resistance regardless of the weight.

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.

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

VERY IMPORTANT !!

Go to slide 44 + 45

Type 2 DM:

- 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 of hyperglycemia (including polyuria, polydipsia, nocturia, blurred vision, and weight loss) are often noted only in retrospect after high blood glucose reading.
- DKA as the presenting symptom of type 2 diabetes is uncommon 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.

VERY IMPORTANT !!

Go to slide 44 + 45

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

Clinical Presentation of Type 2 Diabetes

This is one of the **most important slides**, and it is likely to be tested in questions. **Most patients** with **Type 2 diabetes** discover that they have the disease **incidentally**, rather than because they develop obvious symptoms. This is largely due to **increased awareness** and more frequent **screening**, whether annually or every 2–3 years, which allows diabetes to be detected before significant symptoms develop. As a result, the number of patients who are **symptomatic at the time of diagnosis** has decreased.

Why Is Type 2 Diabetes Often Asymptomatic?

The appearance of symptoms depends largely on the **degree of hyperglycemia (pathophysiology)**. For example, a patient with a fasting plasma glucose around **125 mg/dL** is unlikely to have noticeable symptoms, whereas when glucose reaches around **200 mg/dL**, symptoms become much more likely. Since Type 2 diabetes usually develops **gradually**, starting with **mild hyperglycemia**, most patients do not initially experience significant symptoms. Therefore, many cases are discovered during routine screening or investigations performed for another reason.

The Classical Symptoms – The Three Ps

The classical symptoms of significant hyperglycemia are:

Polyuria → excessive urination
Polydipsia → excessive thirst
Polyphagia → excessive hunger

Weight loss is also an important manifestation of significant insulin deficiency and hyperglycemia. These symptoms are generally **less likely to appear when hyperglycemia is mild**, which explains why they are less commonly seen at the initial diagnosis of Type 2 diabetes.

Diabetic Ketoacidosis in Type 2 Diabetes

Although diabetic ketoacidosis (DKA) is classically associated with Type 1 diabetes, it can also occur in Type 2 diabetes. Its occurrence **depends mainly on the availability of insulin**. However, DKA is **not the usual** initial presentation of a typical Type 2 diabetic patient.

Clinical Presentation of Type 1 Diabetes

Type 1 diabetes behaves differently because, by the time of diagnosis, there is usually near-complete destruction of the pancreatic β-cells, resulting in a much more severe insulin deficiency. Consequently, **hyperglycemia is usually more prominent,** and the **three Ps**—polyuria, polydipsia, and polyphagia—are more likely to be present at the initial diagnosis. Therefore, unlike Type 2 diabetes, which is frequently discovered incidentally, Type 1 diabetes is more commonly diagnosed because the patient develops obvious symptoms.

Weight Loss in Type 1 Diabetes

The most common initial presentations of Type 1 diabetes is weight loss accompanied by other catabolic symptoms. The key reason for this weight loss is absolute **insulin deficiency**. Insulin is an anabolic hormone, so when insulin is deficient, anabolic processes decrease while catabolic processes increase. This leads to breakdown of stored energy, including fat and protein, resulting in weight loss.

Important exam point: If asked **why a patient with Type 1 diabetes loses weight,** the answer is:

Insulin deficiency → ↓ anabolism + ↑ catabolism → weight loss.

Do **not answer insulin resistance,** because insulin resistance is not the primary mechanism responsible for the characteristic weight loss in Type 1 diabetes.

Therefore, in a patient presenting with newly diagnosed Type 1 diabetes, the two important clinical presentations to remember are **symptomatic hyperglycemia** and **DKA**, with DKA being the **second most common presentation** according to the lecture.

Diabetic Ketoacidosis in Adults VS Children

If it was in an adult, it's mostly because he is **not compliant to therapy of type 1 diabetes.**

However, a child initially doesn't know that he is diabetic and asymptomatic and euglycemic, then **abrupt DKA presentation**.

Hyperosmolar Hyperglycemic State (HHS)
We have something that is called **hyperosmolar hyperglycemic state**. This is a state that happens in **type 2 diabetic patients**, a hyperglycemic crisis without ketoacidosis. It is considered rare worldwide, but unfortunately in our society it is common. The level of glucose might be more than **300**.

And we should know something regarding **type 2 diabetes**. When high glucose enters pancreatic cells, it causes destruction, so low insulin production (glucotoxicity) and results in **DKA-like symptoms**, especially when superimposed with stress, like infection or acute illness.
And you should know also that **LADA might be present with DKA, but not MODY**.

American Diabetes Association criteria for the diagnosis of diabetes

VERY IMPORTANT

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).

These tests are only to diagnose type 1 and 2, not for gestational diabetes that has another numbers and criteria.

You should know something very important before discussing them:
2 positive tests of these four are needed for diagnosis of asymptomatic patient.
However, if a symptomatic patient came to the clinic, having the three P's (the symptoms that we discussed earlier), or a hyperglycemic crisis (HHS or DKA), & we tested the blood glucose level, which is called random, and it was more than or equal to 200, this is sufficient for diagnosis.
So these two conditions must be met in order to diagnose it.
Numbers are very important here:

- **6.5% is diagnostic for diabetes.**
- **126 fasting plasma glucose is also diabetic, not pre-diabetic.**
- **200 on the OGTT is also diagnostic.**

However, OGTT is the least one used because it's not convenient.

Positive random plasma glucose alone for asymptomatic patients is not sufficient for diagnosis, it must be combined with another test.

Thank you

رسالة من الفريق العلمي:

آية كريمة، حديث شريف..
دعاء أو نصيحة..
أي شيء بدك توصله لدارس الملف
لا تتركها فارغة واكسَب الأجر.

Reference Used:
(numbered in order as cited in the text)

1. First reference
2. Second reference
3. …

Extra References for the Reader to Use:

1. Video
2. Webpage
3. …

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			