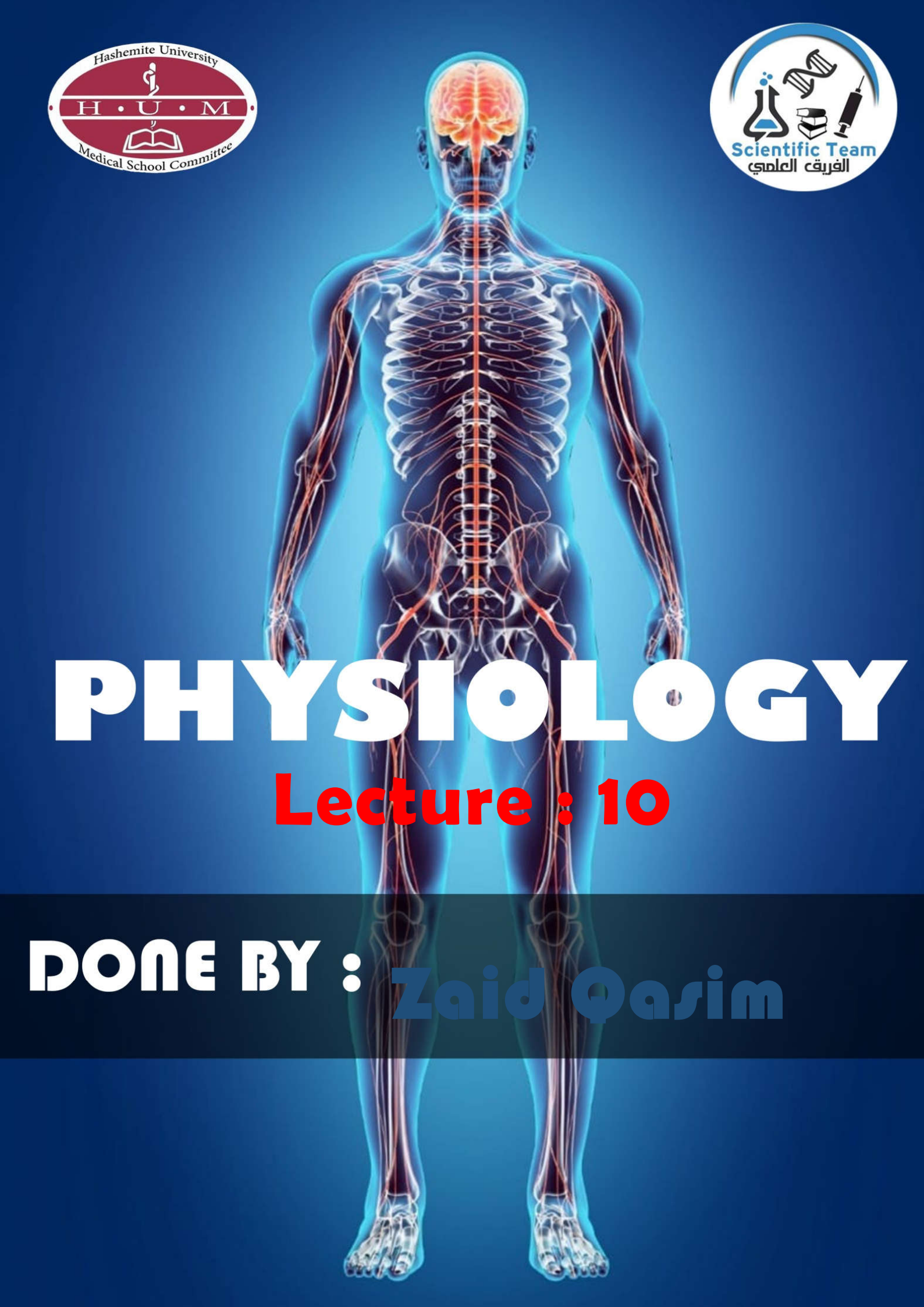

PHYSIOLOGY

Lecture : 10

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بسم الله الرحمن الرحيم

Lecture 10: Diabetes Mellitus And The Metabolic Syndrome

- Diabetes Mellitus (DM) is one of the most common & important endocrine diseases. In this lecture we will discuss the two types of diabetes mellitus(DM) , physiology of diagnosis of (DM) and treatment of diabetic patients.

- (DM) is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either LACK of insulin secretion (type I) or DECREASED SENSITIVITY of the tissues to insulin (type II).

بما إننا أخذنا موضوع السكري في الفارما ، فإن شاء الله تعالى الكلام هون رح يكون سهل ومر علينا من قبل . . .

- There are **TWO** general types of diabetes mellitus:

1. Type I diabetes, also called **insulin-dependent diabetes mellitus**, is caused by lack of insulin secretion. It is the result of β-cell destruction. It accounts for less than %5of cases.

2. Type II diabetes, also called **non-insulin-dependent diabetes mellitus**, is initially caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called insulin resistance. It accounts for more than 80-90% of diabetes cases. It is usually associated with obesity in adults and is characterized by mild hyperglycemia.

- In both types of diabetes mellitus, metabolism of all the main foodstuffs (carbohydrates, fats and proteins) is altered. Glucose uptake and metabolism by most cells of the body, *except those of the brain*, is prevented. As a result, blood glucose concentration increases and utilization of fats and proteins increases.
- This metabolic alteration results in **increased plasma osmolarity** and **urinary loss of glucose**, accompanied by **excess loss of water and sodium** (**polyuria**).

- The resulting dehydration triggers compensatory mechanisms such as **thirst** (**polydipsia**).
  The inability of the cells to utilize glucose resembles a state of **cellular starvation, stimulating hunger** (**polyphagia**) and triggering the activation of compensatory responses to increase the release and availability of fuel substrates through **activation of lipolysis and proteolysis.**

- Lack of insulin results in **increased circulating levels of free fatty acids and gluconeogenic amino acids**. These exceed the liver's capacity for their metabolic utilization, leading to the **buildup of ketone bodies** in the blood (**diabetic ketoacidosis**) and their urinary excretion.

1- Type 1 DM (Insulin-dependent DB or IDDM).

- It could result from viral infection or autoimmune disorders that affect β cells (type 1A immune-mediated) and autoantibodies against β cells can be isolated from serum of the patient, **OR** due to hereditary tendency for β cell degeneration (type 1B idiopathic or non– immune-related).
- In the United States and Europe, approximately %90to %95 of people with type I DM have type 1A immune-mediated diabetes.

- Type 1A can occur at any age, but ...
- The usual onset is during childhood therefore, it is sometimes called **juvenile diabetes mellitus**. However, type I diabetes can occur at any age, including adulthood, following disorders that lead to the destruction of pancreatic beta cells.

- Approximately %3to %4of children develop type I diabetes when a parent has the disease (insignificant percentage).

- Main treatment is achieved by insulin intake. Type I diabetes is characterized by the development of **ketoacidosis** (uncontrolled production of ketone bodies) and **metabolic acidosis** (body's acid-base balance in which there is an increased in the acid concentration in the body) in the absence of insulin therapy due to increased fat utilization (within hours).
- Type I diabetes require **exogenous insulin** replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis. There are different insulin preparations and regimens used in treatment of (type I DM).
- **Remember:**
  - *High doses of insulin must not be ever taken in night before sleep because the severe hypoglycaemia risk during sleep may result in severe complications and even, may cause death.*

- *Insulin is a polypeptide that is vulnerable to digestion by the proteolytic enzymes of the gastrointestinal tract, so it is given most commonly in the form of subcutaneous insulin injections.*

- Glucose spills into the urine (*glucosuria*) when blood glucose concentration rises above **180mg/dl** (=the threshold).
  - Glucose can reach up to 1200 mg/dl within few days or weeks in the absence of insulin administration.

- *Renal threshold of glucose (RTG)* is the concentration of blood glucose above which the proximal tubule of the kidney becomes overwhelmed and begins to excrete glucose into the urine. It equals 160-180 mg/dl.

- The absence of glucose in the urine doesn't necessarily indicate that the patient doesn't have diabetes mellitus since blood glucose can rise highly but still below the RTG i.e. blood glucose > 125mg/dl but < 180mg/dl. *So, we depend on blood glucose rather than glucose concentration urine in the diagnosis of DM.*

- High glucose →dehydration & **osmotic diuresis** (due to glucosuria) →intracellular and extracellular dehydration + thirst sensation.

- Chronic high glucose (in case of poor treatment or improper control)→structural change in blood vessels and inadequate blood supply to the tissues →→→
  - MI or CVA.
  - End-stage kidney disease.
  - Retinopathy and blindness, and
  - Limb gangrene (may require amputation!)
  - Also it can lead to peripheral neuropathy (Somatic nervous system dysfunction including numbness, weakness, pain and decreased sensation in the extremities). Diabetic patients with such complication won't respond to the tingling in their limb. Also, due to the impaired blood supply they're very susceptible to bacterial infections which may result in a severe limb complication, the so-called diabetic foot.
- Autonomic nervous system dysfunction with :
  - Impaired CVS reflexes like Baroreceptor Reflexes which is accompanied by postural hypotension.
  - Impaired bladder control.

- This type of DM is commonly associated with:
  - Hypertension, secondary to renal injury in which impaired blood supply to the kidney will result in increased Renin and Angiotensin II secretion and hypertension.

- Atherosclerosis secondary to abnormal lipid metabolism.

2- Type 2 DM (Non-insulin-dependent DB or NIDDM).

- Have the same metabolic abnormalities as Type I, but it rarely leads to ketoacidosis. Type II diabetes is often a consequence of "syndrome X" or "insulin-resistance syndrome", or metabolic syndrome.

- Approximately 80% to %90of people with type II diabetes are overweight.

> Body mass index (**BMI**) = body wt. (Kg)/ length (meter) square.
> In normal adults = 20 -25 kg/m2.
> Overweight when 30> BMI > 25.
> Obesity when BMI >30 kg/m2.

- When a person gains more weight, insulin receptors and the insulin receptor sensitivity to insulin DECREASES and insulin resistance may occur.

➢ *Features of the metabolic syndrome include:*

1. Obesity, especially accumulation of abdominal fat (**central obesity).**
2. Insulin resistance.
3. Fasting hyperglycemia.
4. Lipid abnormalities, such as ***increased*** blood triglycerides, ***decreased*** blood high-density lipoprotein-cholesterol (HDLP) and ***increased*** blood low-density lipoprotein-cholesterol (LDLP).
5. Hypertension and atherosclerosis with abnormal function of the vascular endothelium.

- The age onset is over 30 years of age. Unlike DM type I, DM type II develops gradually, and the disease develops gradually, therefore it is called sometimes **adult onset diabetes**.

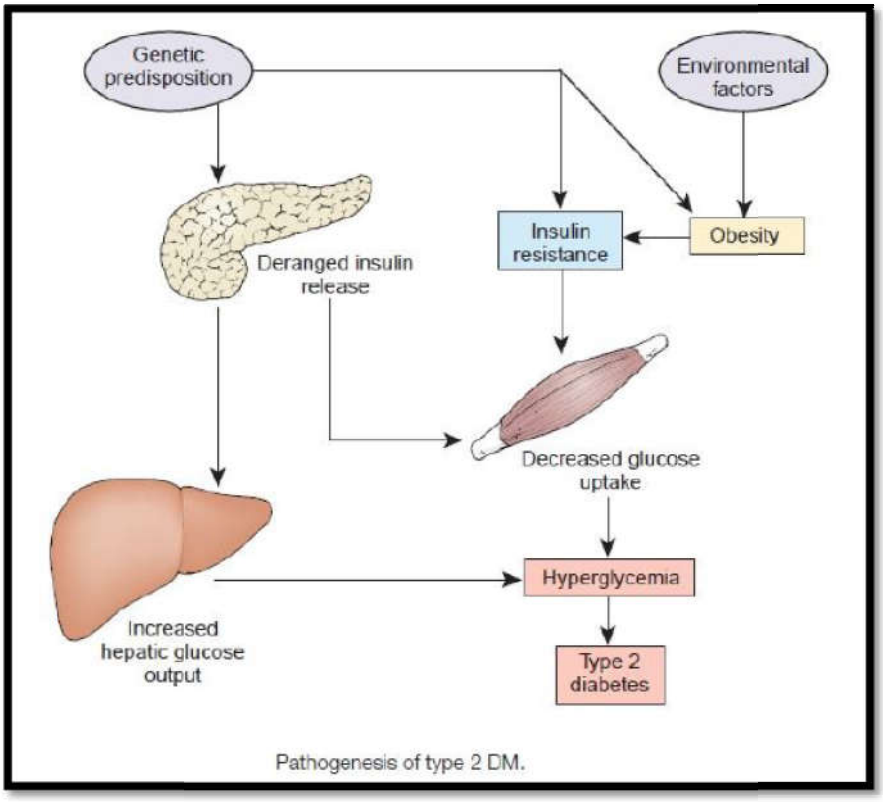
➢ Type II diabetes has a strong genetic component. People with one parent with type II diabetes have an increased risk for developing the disease.
- If both parents have the disease, the risk is approximately 40%.

- In contrast to type I, type II is associated increased plasma levels of insulin concentrations. ***Hyperinsulinemia*** occurs as a compensatory response by the pancreatic beta cells for insulin resistance.
- *We can differentiate between the two types of DM by measuring the insulin concentration in the plasma; a patient with DM type II will have high level of*

insulin in contrast to a patient with DM type I whose plasma insulin will be abnormally very low.

- Despite fasting Hyperinsulinemia, hepatic insulin resistance is manifested by overproduction of glucose (i.e. *continued* glycogenolysis) → elevated fasting blood sugar (*Hyperglycemia* and *Hyperinsulinemia*).

- This figure summarizes the pathogenesis of type II DM. Notice that hyperglycaemia is resulted from both: decreased glucose uptake by body tissues and increased hepatic glucose output due to glycogenolysis.



Pathogenesis of type 2 DM.

- Late in the disease, β cells become exhausted and are unable to produce enough insulin to prevent more severe hyperglycemia especially after starchy meal.
- Insulin resistance is secondary to obesity. Mechanism of this is unknown, it could be due to down regulation of insulin receptors in skeletal muscle, liver, and adipose tissue. Therefore, one of the most important factors in the early treatment of DM is to decrease body weight.
- How much pancreas can stand till it gets exhausted is genetically determined. Those who can sustain do not develop clinically significant DM for many years although they have increased insulin plasma level.

مريض عنده فقط أبوه المُصاب بضل البنكرياس عنده شغال أكثر من مريض عنده أبويه الاثنين مُصابين وهكذا..

وهاي مش قاعدة مطلقة بس بتضل تنطبق على الأشخاص الي عندهم Genetic predisposition...

- It has been estimated that 10% of of pancreas are lost every year in an uncontrolled or untreated patient type 11 DM i.e. in an untreated patient with type II DM all β cells will die after 10 years and the patient therefore, may require administration of insulin.

- Because patients with type II diabetes do not have an absolute insulin deficiency, they are less prone to ketoacidosis compared to patients with type I diabetes. (ketoacidosis is rare in a patient with type II diabetes).

- It is not recommended to give a child with type I DM high insulin dose since hypoglycemic attacks is very common in this age group.{Also, a child who moves or play a lot will have increased glucose uptake by his skeletal muscles}.
  فلذلك بنعطيه إنسولين كافي لينزل الغلوكوز في الدم لحد الـ 120 أو الـ 140 ، والطفل لما يلعب رح ينزله للـ 100 (;

- ***Gestational diabetes*** is a special type of type II DM, in which the pregnant women show the signs& symptoms of type II DM that subsides and disappears after delivery. It results from increased prostaglandins level in the pregnant women which may cause diabetes and insulin resistance. Most of women who have suffered from gestational diabetes will have type II DM after 20-25 years.

- In the early stages, type II diabetes can be effectively treated with exercise, caloric restriction, and weight reduction, and no exogenous administration of insulin is required.

- Drugs such as *thiazolidinediones* and *metformin* increase insulin sensitivity. *Sulfonylurea* causes additional insulin release.
- New Drugs that mimic the actions of the *incretin GLP-1* have been developed to enhance the secretion of insulin and are intended to be used in conjunction with other antidiabetic drugs. Another therapeutic approach is to inhibit the enzyme which inactivates GLP-1 and GIP (Gastric Inhibitory Polypeptide). Then the effects of GLP-1 and GIP can be prolonged, leading to increased insulin secretion and improved control of blood glucose levels.

كل هاي الأدوية إن شاء الله إنكم بتعرفوها و كيف بتشتغل من الفارمـا...

Physiology of diagnosis of DM.

- The usual methods for diagnosing diabetes are based on various chemical tests of the urine and the blood. *These tests include the following:*

(1) Urinary glucose can be estimated by a **urine dipstick** test or more complicated quantitative laboratory tests may be used to determine the quantity of glucose lost in the urine.
هو باختصار عبارة عن stick يغمس في البول ويعطي تغيرات في اللون مختلفة بالنسبة إلى كمية الغلوكوز الموجودة...
الدكتور ما ركز عليه كثير.

- A normal person loses undetectable amounts of glucose in the urine. A person with diabetes loses glucose in small to large amounts, in proportion to the severity of the disease and the intake of carbohydrates.

Feature	Type 1	Type 2
Age at onset	Usually <20 yr	Usually >30 yr
Body mass	Low (wasted) to normal	Visceral obesity
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

Clinical Characteristics of Patients with Type 1 and Type 2 Diabetes Mellitus

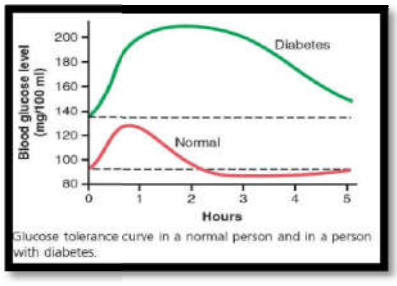
- Also, **keto acids** can be detected by dipstick test in the urine, and their quantitation aids in determining the severity of the diabetes.

(2) Fasting Blood Glucose and Insulin Levels. The fasting blood glucose level in the early morning is normally **70to 90 mg/100 ml**, and **110mg/100 ml** is considered to be the upper limit of normal. Above this value often indicates diabetes mellitus or at least marked insulin resistance.

- As we talk before, with type I diabetes, plasma insulin levels are very low or undetectable during fasting and even after a meal. In persons with type II diabetes, plasma insulin concentration may be several fold higher than normal.

- This test may be not useful for the diagnosis for diabetes when the patient refrains from food for 11-12 hours because blood glucose level falls into normal range within 6 or 7 hours in such patient.

(3) Glucose Tolerance Test. When a normal person ingests 1gram of glucose/Kg body wt orally → Blood glucose should normally rise to 120-140mg/dl and back to normal within 2hours**.** In a person with diabetes, the fasting blood glucose concentration is almost always above 110mg/dl. After ingestion of glucose, these people exhibit a much greater than normal rise in blood glucose level (more than 120- 140mg/dl) and the glucose level falls back to the control value only after 4to 6hours**.**



Glucose tolerance curve in a normal person and in a person with diabetes.

(4) Glycated Hemoglobin Test (HbA1c) for chronic glycemia. This test was added to the list of diagnostic test for diabetes in 2009. Glycosylation of hemoglobin is proportionate to blood glucose concentrations. Because the half-life of erythrocytes is approximately 60days, the level of glycated haemoglobin reflects the prevailing mean blood glucose concentration over the preceding 8–6weeks; providing a measure of chronic glycemia. Normal values are **%5** and targeted values in diabetic patients in treatment is **< 7%**. In prediabetic patients the value will be **>%5** and **<7%**.

Treatment of Diabetes Mellitus

- Treatment of type I diabetes mellitus requires administration of insulin.

- In the past, porcine and bovine insulin were used to treat patients with diabetes. Currently, human recombinant insulin is available and has replaced animal derived insulin, avoiding problems such as the development of antibodies to nonhuman insulin.
- Insulin is available in several forms. "Regular" insulin has a duration of action that lasts from 3 to 8 hours, whereas other forms have effects that last as long as 10 to 48hours.

- In persons with type II diabetes, dieting and exercise are the first choice in an attempt to induce weight loss and reverse the insulin resistance.
- If this strategy fails, drugs may be administered to increase insulin sensitivity (such as metformin) or to stimulate increased production (such as sulfonylureas) of insulin by the pancreas.
- To avoid abnormalities of fat metabolism, most physicians also prescribe lipid-lowering drugs to help prevent these disturbances.

Test question:

Q. A 57-year-old-diabetic patient is brought to the emergency room with history of frequent urination, weight loss, and decreased oral intake. The patient is lethargic, dehydrated, hypotensive, and tachycardic. The patient was recovering from a recent bout of pneumonia. Which of the following laboratory findings are likely?

A. Plasma glucose of 40 mg/dl.
B. Plasma osmolarity >350 mOsm/l.
C. Low blood pH.
D. High plasma ketones.
E. Low blood insulin concentration.

- *The right answer is* **B** *because the patient has type II DM and all other choices aren't compatible with the disease. He suffered from pneumonia because his immunity is low and he is susceptible to infection as we talked above. Both blood glucose and insulin will be high (Hyperglycemia and Hyperinsulinemia) and the risk of ketoacidosis and low pH is rare in such patient. Remember that : High blood glucose →dehydration &* ***osmotic diuresis*** *(due to glucosuria) →intracellular and extracellular dehydration + thirst sensation.*

... I'm sorry for any unintended mistake

- Other test questions :

(1) Which of the following are incorrectly paired?

A. B cells: insulin
B. D cells: somatostatin
C. A cells: glucagons
D. Pancreatic exocrine cells: chymotrypsinogen
E. Fcells: gastrin

(2) Which of the following are incorrectly paired?

A. Epinephrine: increased glycogenolysis in skeletal muscle.
B. Insulin: increased protein synthesis.
C. Glucagon: increased gluconeogenesis.
D. Progesterone: increased plasma glucose level.
E. Growth hormone: increased plasma glucose level.

(3) Which of the following would be least likely to be seen 14 days after a rat is injected with a drug that kills all of its pancreatic B cells?

A. A rise in the plasma H concentration.
B. A rise in the plasma glucagon concentration.
C. A fall in the plasma HCO, concentration.
D. A fall in the plasma amino acid concentration.
E. A rise in plasma osmolality.

(4) Insulin increases the entry of glucose into:

A. All tissues.
B. renal tubular cells.
C. the mucosa of the small intestine.
D. most neurons in the cerebral cortex.
E. skeletal muscle.

(5) A meal rich in proteins containing the amino acids that stimulate insulin secretion but low in carbohydrates does not cause hypoglycemia because:

A. the meal causes a compensatory increase in T, secretion.
B. cortisol in the circulation prevents glucose from entering muscle.
C. glucagon secretion is also stimulated by the meal.
D. the amino acids in the meal are promptly converted to glucose.
E. insulin does not bind to insulin receptors if the plasma concentration of amino acids is elevated.

Answers:
1- E.
2- D.
3- D.
4- E.
5- C.

"مَن يسأل النّاس يحرموه
وسائل الله لا يخيب"