DIABETES MELLITUS AND THE METABOLIC SYNDROME

Dr. Waleed R. Ezzat

LECTURE OBJECTIVES:

1. Identify the disease states caused by over-secretion, under-secretion, or decreased sensitivity to insulin, and describe the principal manifestations of each.
2. Understand the major differences between type I and type II diabetes.
3. Define the metabolic syndrome and describe its associations with the development of type II diabetes.
4. Describe physiological changes in diabetes mellitus type I and type II
5. Explain how both genetic and non-genetic factors can impair insulin responsiveness.
6. Discuss complications of diabetes from physiological perspective
7. Explain how mechanistic aspects of the incretin effect have led to a new class of antidiabetic drugs.

DIABETES MELLITUS (DM)

- Def.: Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either ***lack*** of insulin secretion or ***decreased sensitivity*** of the tissues to insulin.
- 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 5% of 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 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.

DIABETES MELLITUS (DM)

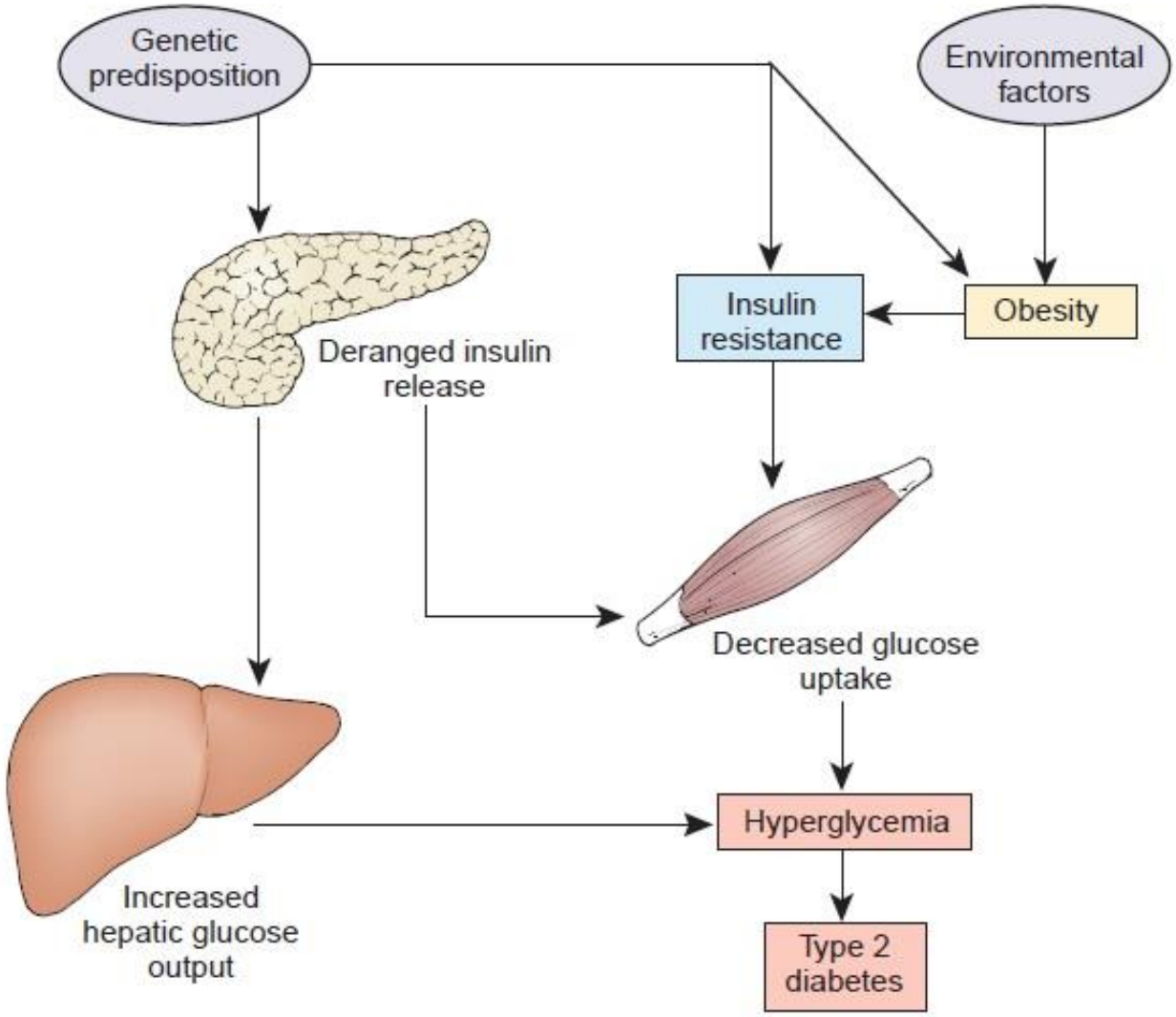
- Type I (The Insulin-dependent diabetes mellitus or IDDM)
  - It could result from viral infection or autoimmune disorders that affect β cells (type 1A immune-mediated), **or** due to hereditary tendency for β cell degeneration (type 1B idiopathic or non–immune-related).
  - In the United States and Europe, approximately 90% to 95% of people with type I DM have type 1A immune-mediated diabetes.
  - The usual onset is during childhood therefore, it is 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 3% to 4% of children develop type I diabetes when a parent has the disease.
  - Type I diabetes is characterized by the development of **ketoacidosis** and **metabolic acidosis** in the absence of insulin therapy due to increased fat utilization.

DIABETES MELLITUS (DM)

- Type I (The Insulin-dependent diabetes mellitus or IDDM) - cont.
  - Type I diabetes require **exogenous insulin** replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis.
  - Glucose spills into the urine when blood glucose concentration rises above **180 mg/dl** (= the threshold). Glucose can reach up to 1200 mg/dl within few days or weeks.
  - High glucose → dehydration & **osmotic diuresis** → intracellular and extracellular dehydration + thirst sensation
  - Chronic high glucose → 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. Also it can lead to peripheral neuropathy & autonomic nervous system dysfunction (impaired CVS reflexes, impaired bladder control, decreased sensation in the extremities, etc.). This type of DM is commonly associated with hypertension, secondary to renal injury, and atherosclerosis secondary to abnormal lipid metabolism.

DIABETES MELLITUS (DM)

- Type II (non-insulin-dependent diabetes mellitus 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 90% of people with type II diabetes are overweight.
  - 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 and decreased blood high-density lipoprotein-cholesterol (HDLP)
    5. Hypertension and atherosclerosis with abnormal function of the vascular endothelium.
  - The age onset is over 30 years of age. It 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.
  - Despite fasting hyperinsulinemia, hepatic insulin resistance is manifested by overproduction of glucose → elevated fasting blood sugar.



Pathogenesis of type 2 DM.

DIABETES MELLITUS (DM)

- Type II (non-insulin-dependent diabetes mellitus or NIDDM) - cont.
  - 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.
  - 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.
  - 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.
  - 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.
  - 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. Then the effects of GLP-1 and GIP can be prolonged, leading to increased insulin secretion and improved control of blood glucose levels.

PHYSIOLOGY OF DIAGNOSIS OF DM

The usual methods for diagnosing diabetes are based on various chemical tests of the urine and the blood.

1. **Urinary Glucose**. A urine **dipstick test** or more complicated quantitative laboratory tests may be used to determine the quantity of glucose lost in the urine. 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.

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

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

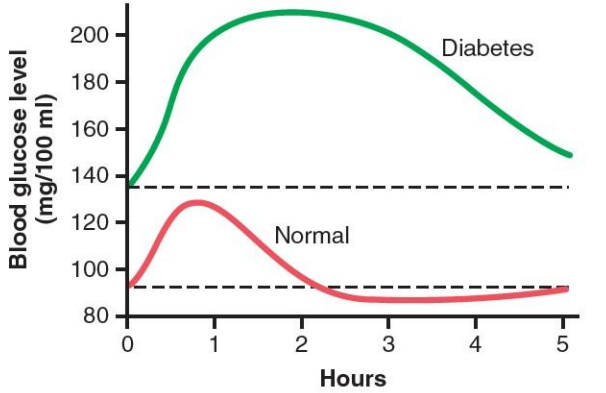
Clinical Characteristics of Patients with Type 1 and Type 2 Diabetes Mellitus

PHYSIOLOGY OF DIAGNOSIS OF DM (CONT.)

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

   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.

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



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

4. **Glycated Hemoglobin Test (HbA1c)**. 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 60 days, the level of glycated hemoglobin reflects the prevailing mean blood glucose concentration over the preceding 6–8 weeks; providing a measure of chronic glycemia. Normal values are **5%** and targeted values in diabetic patients in treatment is **<7%**.

TREATMENT OF DIABETES

- 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 48 hours.
- 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.