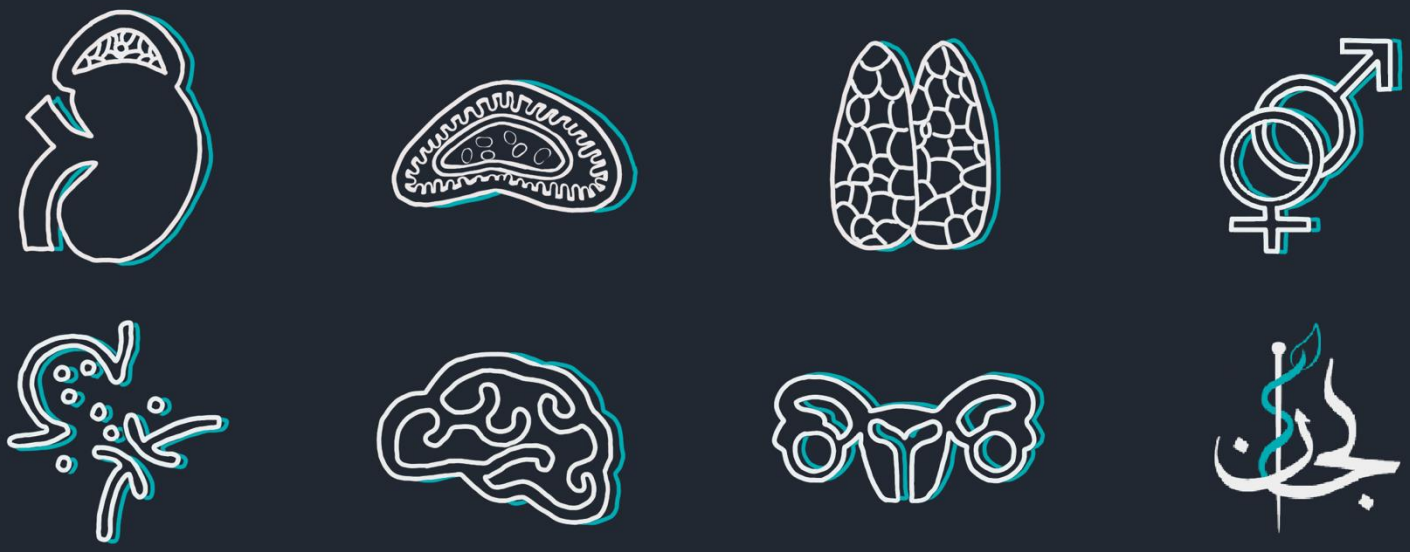
Endocrine PATHOLOGY



Title: Sheet 6 - Diabetes Mellitus

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In this lecture we will be talking about pancreatic secretions and diseases that target/effect the secretions of the pancreas.

Before we start our lecture, we shall have a quick recap in the biochemistry regarding pancreatic endocrine secretions which consists of Insulin and Glucagon.

Insulin VS. Glucagon

1-

Insulin: ➔The main **function** of insulin is to increase the rate of glucose transport into certain cells in the body. In other words, it facilitates the entry of glucose particles into our cells so that they get degraded, producing energy (thus regulating glucose levels in the blood).

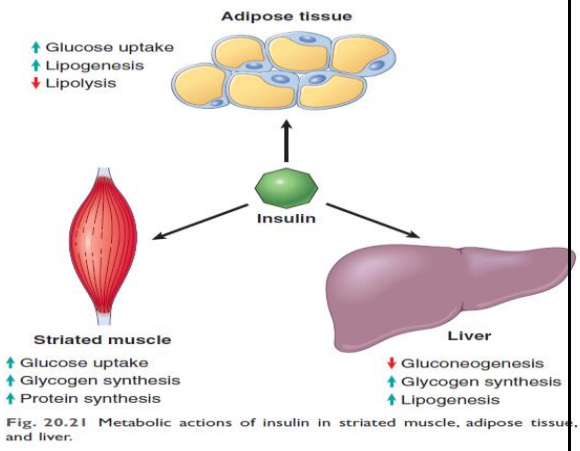


Fig. 20.21 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

➔Insulin is secreted when the body is in a high energy state (that is after having a fatty meal).

➔Has anabolic effects on lipids (induces lipogenesis), glycogen (glycogenesis), and proteins (insulin induces protein uptake and synthesis).

➔Reduces production of glucose from the liver (inhibits gluconeogenesis)**.**

➔**Inhibits the hormone-sensitive lipase** (very important). Therefore, any lack of secretion of insulin will contribute to a failure of the inhibition➔increased lipolysis!.

*****Any deficiency in insulin production leads to a lack in the functions we mentioned above.**

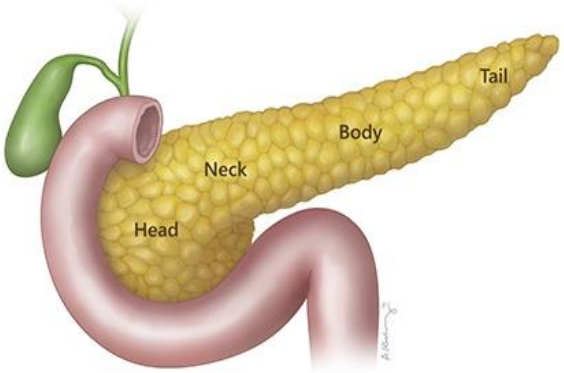
2-Glucagon:➔The main function of glucagon is to facilitate the breakdown of stored glycogen in liver to glucose, increasing the blood glucose levels in the body (so glucagon also takes part in regulation of glucose levels in the blood).

➔**Opposes Insulin**: -It has a catabolic effects on lipids (induces lipolysis), glycogen (glycogenolysis), and proteins (induces breakdown of proteins into amino acids).

- It is secreted in low energy state conditions.
- It increases production of glucose from the liver (induces gluconeogenesis).
- **It activates the hormone sensitive lipase**.

Now let's start with our lecture: **(00:00)**

Pancreas

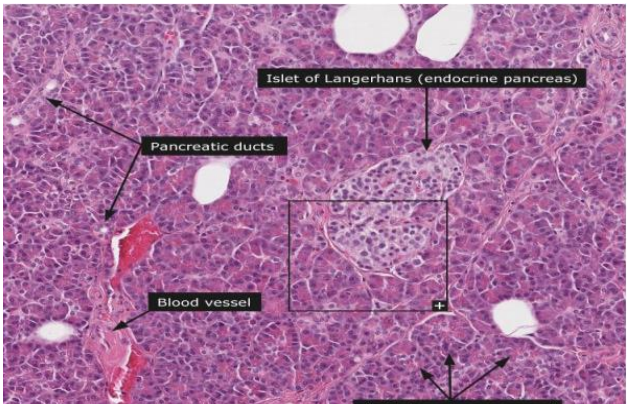


This figure shows the parts of the pancreas and it is relations to other systems, particularly the digestive system.

- Before talking about functions of the pancreas and its role in homeostasis, we should know that there are two types of secretions in the pancreas:

1- Exocrine secretion➔ Which is dedicated to secreting digestive enzymes through glands and ducts.

2- Endocrine secretion➔ Which is dedicated to secreting hormones (such as insulin) through the islets of Langerhans.



This is a histological section taken from the pancreas showing exocrine and endocrine regions. Note that the islets of Langerhans appear in clusters and are pale in color. Also it is obvious that the exocrine region is **basophilic**.

- **Contents of the islets** : It contains several types of hormones, mainly three types:
  Alpha cells➔ Secretes glucagon.
  Beta cells➔Secretes insulin.
  Delta cells➔ Secretes somatostatin (suppressor of insulin and glucagon secretion).

- Up to now we know the function of insulin and from which organ and cell type it is produced. Now, it is really important to know that insulin should be secreted in specific amounts. So, any defect in its secretion or in the amount of secretion will absolutely contribute to a disease. That disease is called **Diabetes Mellitus!**

Diabetes Mellitus (D.M) (2:20)

-Defined as a group of metabolic disorders that leads to hyperglycemia.
-Normal glucose levels in the blood are between 70-120mg/dl
-This level is maintained by the balance between insulin and glucagon.

Diagnosis:

1- Fasting blood glucose levels ≥ 120 mg/dl
2- A random plasma glucose ≥ 200mg/dl (this criteria only applies if patient has signs of hyperglycemia. (such as polyuria, polydipsia)
3- Oral glucose tolerance test: This test is made by giving the patient 75mg of glucose and measuring his plasma after 2 hours of ingesting the glucose dose. If his plasma glucose is ≥200mg/dl, then he is a diabetic!
4- Glycated hemoglobin (السكر التراكمي), also called (**hbA1c**), is greater than or equal to 6.5%.

**Notice that D.M might occur at once or at stages. The stage that might precede D.M is called the prediabetic state.

Prediabetes:

-Defined as impaired glucose tolerance .
-Manifested by elevated blood sugar levels that does not reach the criteria for diagnosis of D.M.
-Prediabetic people have higher risk of developing frank diabetes!

Diagnosis:

1- Fasting blood glucose levels: **(100≤[glucose]≤125).mg/dl**
2- 2-hour plasma glucose levels: **(140≤[glucose]≤199).mg/dl**
3- HbA1c level between **5.7 and 6.4 %.**

*Note that 25% of prediabetic patients will develop frank diabetes in the next 5 years!

Very important note: In cases of acute stress, many hormones are secreted such as **catecholamines (epinephrine) and **cortisol,** which oppose insulin. This causes transient hyperglycemia. Therefore, those individuals have a higher risk of developing D.M than others if the stress is not treated .

***Stress includes severe infections, traumas, and burns.

***Diagnosis of D.M in these cases requires persistence of hyperglycemia following resolution of the acute stress.

- **Classification of D.M:** **(8:30)**

A- **Type 1 D.M: Absolute deficiency of insulin** due to destruction of islets by autoimmune mechanisms. In other words, an inflammatory reaction occurs between immune cells and the cells of Langerhans, leading to destruction of the Langerhans cells and consequently destruction of insulin producing cells (β cells).

B- **Type 2 D.M: Relative insulin deficiency** - In this type, there is production of insulin, but it is not enough to decrease blood glucose levels.

Other causes:

C- Genetic defects of beta cell function: The best example is the **MODY disease** (**M**aturity **O**nset **D**iabetes of the **Y**oung) which is manifested by insulin gene mutations (genetic defects that affect insulin synthesis, so a non-functional insulin will be produced) or defects in proinsulin conversion.

D- Genetic defects in insulin action: In this case intact insulin is produced, but the insulin receptors are mutated, so no proper binding between insulin and its receptor occurs. So, we won't get the desired effect of insulin.

E- Gestational diabetes: Occurs in pregnant women.

F- Exocrine pancreatic defects: Such as chronic pancreatitis (inflammation that takes place in the pancreas leading to destruction of other pancreatic cells, including beta cells).

G- Endocrinopathies: Including acromegaly, Cushing syndrome, and pheochromocytoma.

H- Infections (CMV, Coxsackievirus B, congenital rubella)

I- Drugs such as steroids.

Pheochromocytomas are neoplasms that synthesize and release **catecholamines.**

Cushing syndrome: A syndrome manifested by elevated **glucocorticoid** levels.

Type 1 vs Type 2 D.M

Type 1 Diabetes Mellitus: (12:20)

- It accounts for 10% of all cases.
- It is an **autoimmune disease** destructing pancreatic beta cells leading to an **absolute** deficiency of insulin.
- Most commonly develops in childhood, becomes manifest in puberty and patients depend on **exogenous insulin** for survival, meaning that without insulin they develop complications.
- The classic manifestations of this disease occur late in its course, after 90% of the beta cells have been destroyed.
- Has genetic predisposition.

Pathogenesis: Since the disease is autoimmune, we shall talk about a bit of immunology. When immune cells are created (particularly T-cells), they are trained not to attack the self-antigens (our cells, tissues, and organs). This is **called self-tolerance**.

In autoimmune disease, self-tolerance fails to takes place. This results in the immune system considering our cells and organs as a threat, thus the immune response is activated and inflammation occurs. Regarding the disease (D.M type 1), the same story occurs but in the beta cells of Langerhans, causing their destruction.

Causes of failure of self- tolerance:

1- Defective clonal deletion of self-reactive T-cells in the thymus.
2- Abnormalities of regulatory T-cells that dampen the effector T-cell responses.

- As a result, **autoantibodies** against B cell antigens, including insulin and enzyme glutamic acid decarboxylase, are formed . These autoantibodies are detected in the blood of 70-80% percent of type 1 diabetic patients**.**

- It has been suggested that viruses play a role in causing the disease…but this is controversial!

Type 2 Diabetes Mellitus**:** (15:45)

- Accounts for 80-90% of cases.
- In type 2 only does insulin resistance takes place.

- **Insulin resistance (I.R)**: A state in which cells don't respond to insulin secreted by the pancreas.

- That means that glucose won't enter these cells , resulting in its accumulation in the blood stream (hyperglycemia).
- This causes more production of insulin, which requires huge effort from Beta cells to do so.
- At the long term, Beta cells become exhausted, meaning that they can't fulfill the body's need for insulin. So, they become dysfunctional, this is known as **Beta cell dysfunction.**

Beta cell dysfunction is manifested as **inadequate** insulin secretion in the face of insulin resistance and hyperglycemia.

- **Essentially: Insulin resistance contributes to beta cell dysfunction!**

- The liver, skeletal muscles, and adipose tissue are the major tissues in which insulin resistance takes place.

Manifestations of Insulin Resistance: The unresponsiveness of cells to insulin will lead to: (17:05)

A- **Decreased uptake of glucose into cells**, leading to a reduction of glycolysis.
B- Failure to inhibit gluconeogenesis in the liver (which means continuous production of glucose), leading to increased fasting blood glucose levels.
C- Abnormally low glucose uptake and glycogen synthesis (glycogenesis).
D- Failure to inhibit hormone-sensitive lipase in adipose tissues, leading to excess production of free fatty acids circulating in the blood.

Obesity and insulin resistance:

- Most type 2 diabetic people are obese (visceral obesity), suggesting that there is a relationship between obesity and diabetes. The more you gain weight, the more your body mass index increases, the higher probability of having insulin resistance, and the higher risk for having type 2 diabetes!

- However, hyperglycemia is not a must for acquiring insulin resistance, meaning that a simple obesity (unaccompanied by hyperglycemia) might lead to I.R, which indicates a fundamental abnormality of insulin signaling in states of fatty excess

- Distribution of fats plays a major role in this. For example: if the fat was distributed in the abdomen (central obesity), then this is more likely to be associated with I.R (increasing the risk of having type 2 diabetes). While if the fat was peripherally distributed (gluteal/subcutaneous) obesity, it is less likely to be associated with I.R.

    - **Treatment**: Treatment includes asking the diabetic patient to lower their food intake, which leads to a decrease in insulin resistance and increase in insulin sensitivity (meaning that cells become more responsive to insulin, thus allowing insulin's desired effect to take place).

- **Metabolic syndrome**: A cluster of conditions that occur together leading to an increased risk for acquiring many diseases including type 2 D.M. (19:57)

- Constellation of findings of metabolic syndrome:
  -Visceral obesity
  -Insulin resistance
  -Glucose intolerance
  -Cardiovascular risk factors (hypertension and abnormal lipid profile (dyslipidemia))

- **Obesity and Insulin resistance**: (21:05)

1- **Role of excess Free Fatty acids**: As we discussed before, I.R induces the excessive production of free fatty acids. These F.F.A's deposit in various tissues in our body (especially muscle/liver tissues) and become intracellular!

- That's dangerous because these intracellular F.F.A's are considered as potent inhibitors of insulin signaling, meaning that they prevent the signal transduction in these cells for insulin hormone, resulting in acquired I.R!

2- **Inflammation:** The excess F.F.As circulating in the blood stream and deposited in organs are considered toxic, thus an immune response is activated, which is mediated by production of a protein called the **Inflammasome**.

- Production of the inflammasome leads to secretion of IL-1β, which mediates the secretion of additional cytokines from macrophages.

- These cytokines act on major sites of insulin action promoting Insulin resistance.

- As we said that in type 2 diabetic patients, F.F.A's are distributed in different organs including the Islets of Langerhans. The existence of F.F.A's induces cytokine production in these islets, which damages them.

- Later on, the damaged cells of Langerhans are replaced by **Amyloid**. Amyloid is chemical compound that is composed as a result of abnormal aggregation of amylin.

Amylin is a chemical compound secreted by β cells of Langerhans.

3- **Role of adipokines**:

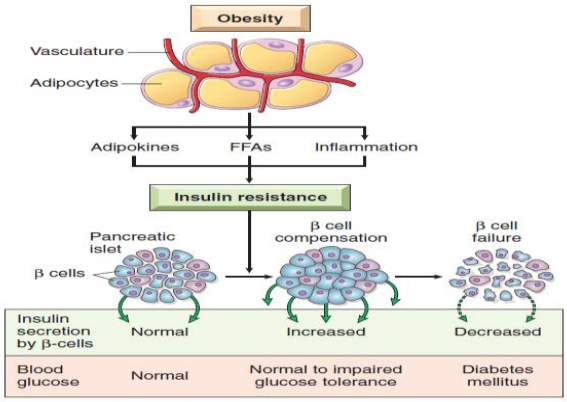
Quick facts about adipose tissue:

- *Adipose tissue is not a passive storage for fat.*

- It is also an endocrine organ that releases hormones in response to changes in the metabolic status.

- A variety of proteins are secreted into the systemic circulation by adipose tissue.
- These molecules are called **adipokines** or adipose cytokines, some of them cause hyperglycemia and others such as **leptin** and **adiponectin** decrease blood glucose by **increasing insulin sensitivity.**

- **In obese people, adiponectin is decreased, leading to a decrease in insulin sensitivity and increase in insulin resistance.**
- **Note that all of the three factors above contribute to the beta cell dysfunction!**



This figure summarizes what we were talking about!

Morphology of D.M

(25:15)

1-**Leukocytes (W.B.Cs) infiltration** of islets: Seen in types 1 and 2 **but is more severe in type 1**, but why? It's because type 1 diabetes is an autoimmune disease➔inflammation takes place. Also, hormone-sensitive lipase is much more activated in type 1 than type 2 ,which leads to more production of F.F.A's circulating in the blood and

organs, which leads to more activation of the immune system and more production of cytokines, thus infiltration is more severe.

***The part written in purple was not said by the doctor, but is written for further clarification!

2-**Reduction of the number and size of islets**, often in type 1 (because it is an autoimmune disease), with rapidly advancing disease.

3-**Amyloid replacement** (**in type 2 only):** Histologically, Amyloid appears as deposition of pink, amorphous material beginning in capillaries between cells.

4-At advanced stages, the islets may undergo **fibrosis.**

**Note that in both types, inflammation is often absent by the time the disease is clinically evident!

This table summarizes what we were talking about!

Type I Diabetes Mellitus	Type 2 Diabetes Mellitus
Clinical	
Onset usually in childhood and adolescence	Onset usually in adulthood; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority of patients are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma
Genetics	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes
Pathogenesis	
Breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by beta cells Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
Pathology	
Autoimmune "insulitis"	Amyloid deposition in islets (late)
Beta cell depletion, islet atrophy	Mild beta cell depletion

HLA, Human leukocyte antigen; *MHC*, major histocompatibility complex.

Clinical features of D.M: (27:00)

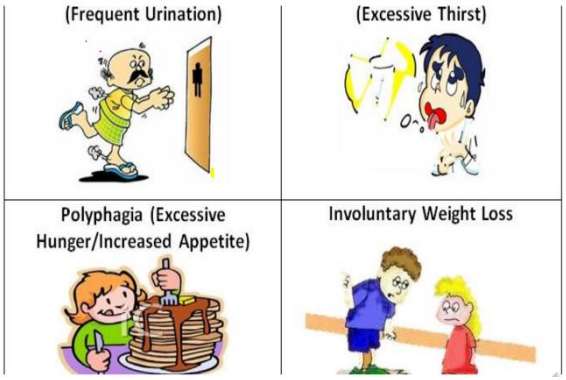
1-As a result of insulin deficiency, glycogen stores in the body are depleted by glycogenolysis.

- The resultant hyperglycemia exceeds the renal threshold for reabsorption.
- The glycosuria induces osmotic diuresis and **polyuria**, causing the loss of water and electrolytes.

Recall that the kidneys have a function in reabsorption of glucose. In diabetics, the kidneys cope with the high amounts of glucose accumulated in blood. This makes it exhausted and thus glycosuria occur.

2-The renal water loss combined with hyperosmolarity (due to hyperglycemia) depletes intracellular water.

- This triggers the thirst center in brain, generating intense thirst **(polydipsia).**



3- Also, as a result of the deficiency of insulin, catabolism of proteins and fats is activated, converting these proteins to amino acids.

- The amino acids proceed to the process of gluconeogenesis, thus these amino acids are converted into glucose.
- That induces a negative energy balance, which in turn leads to increasing appetite **(polyphagia).**

4-Involuntary weight loss.

Acute complications of D.M: (28:47)

Ketoacidosis: Most common in type 1 (why?) As we said previously, hormone-sensitive lipase is more activated in type 1, leading to formation of high quantities of F.F.A's, these F.F.A's are oxidized in the liver, producing ketones.

- In patients with type 1 diabetes, unusual physical activity, infection, or any other form of acute stress worsen the metabolic imbalance leading to diabetic ketoacidosis.

- **Pathogenesis of ketoacidosis**: The plasma glucose is in the range of 500 to 700mg/dl because of absolute deficiency of insulin and unopposed effects of counterregulatory hormones (epinephrine and glucagon). At that time the body is in a **low energy state**, thus producing ketones for energy

- Thus, ketogenesis is an adaptive phenomenon in times of **starvation,** where ketones are generated as a source of energy for consumption by vital organs (such as the brain).

- The rate of which ketones are formed may exceed the rate at which they can be used by peripheral tissues leading to ketonemia and ketonuria.
- If the urinary excretion of ketones is compromised by dehydration, then accumulating ketones decrease blood PH, resulting in **metabolic acidosis.** This may lead to coma.
- In type 2 diabetes, the acute complication is **non-ketotic coma**.

Long-Term Complications of D.M: (31:31)

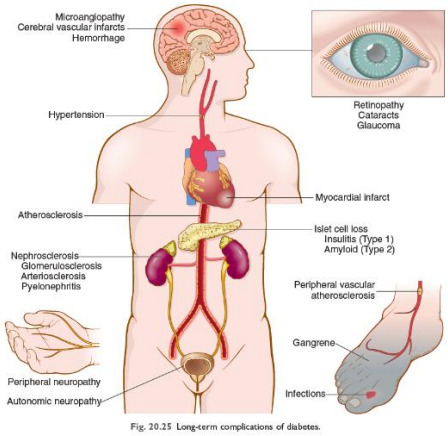


Fig. 20.25 Long-term complications of diabetes.

1-**Blood vessels complications** including: **Atherosclerosis**, **hyaline arteriosclerosis** and **microangiopathy.**

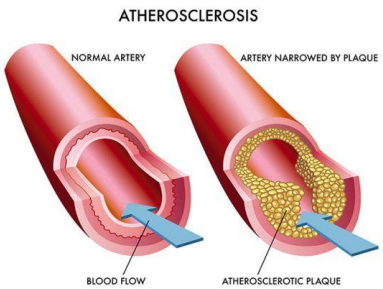
2-**Nephropathy** - including: **Glomerular lesions**, **arteriosclerosis, and pyelonephritis.**

3-**Ocular complications** **including: retinopathy, cataracts and glaucoma.**

4-**Neuropathy**

1-**Blood vessels**:

A-Atherosclerosis:



- The hallmark is accelerated atherosclerosis that affects the aorta and large and medium sized **arteries**.
- It is more severe with early onset in diabetics than non-diabetics.
- Atherosclerosis starts with the formation of an atherosclerotic plaque, which consists of **fibrous tissue** and **lipids.**

- The Atherosclerotic plaque might ulcerate in the coronary artery (supplies the heart with blood), resulting in superimposed thrombus. (خثرة)
- The superimposed thrombus leads to **occlusion**/blockage of the coronary artery, resulting in **myocardial infarction.**
- **Myocardial infarction is considered the main cause of death in diabetic patients, and is as common in diabetic women as in diabetic men.**
- **In the general population, myocardial infarction is common in males than females.**
- **Very important note: Myocardial infarction is not specific for Diabetes!**
- Also, occlusion/blockage of arteries (particularly in lower limb) might lead to **ischemia**, thus increasing the risk for acquiring **dry gangrene**

- If superimposed bacterial infection takes place, then that might cause **wet gangrene.**

- Also, gangrene is **not specific** for diabetics and might occur in other conditions.

- Gangrene of lower extremities is 100 more common in diabetics than general population! ➔Meaning that if somebody has diabetes, he has higher probability for developing gangrene!

B-Hyaline arteriosclerosis: (35:55)

➔Is the vascular lesion associated with **hypertension** in the **arterioles**.

➔Is both more prevalent and more severe in diabetics than in nondiabetics**, but it is not specific for diabetes or hypertension** . it might be seen in elderly persons who don't suffer from either diabetes or hypertension.

➔It takes the form of hyaline thickening of the wall of the arterioles by a hyaline material(eosinophilic material), which causes narrowing of the lumen of that arteriole➔ischemia of organs!

➔In diabetic patients, it's severity is related not only to the duration of the disease but also to the **presence or absence of hypertension**. So, if the diabetic individual has hypertension, then it might makes things worse !

C-Diabetic microangiopathy: (38:15)

➔Defined as diffuse **thickening of the basement membranes**, most evident in the **capillaries** of the skin, skeletal muscle retina, and renal glomeruli.

➔Although they are thickened, they are not functional.

➔It may be seen in renal tubules, nerves, and placenta.

➔It underlies the development of diabetic nephropathy (which may lead to end-stage renal disease), retinopathy (which may lead to blindness), and some forms of **neuropathy.**

2- **Diabetic Nephropathy**: (39:41)

- **Lesions found in the case of nephropathy are**:

A-**Glomerular lesions**, like any lesions that occur in autoimmune glomerulonephritis.

B-**Renal atherosclerosis and arteriosclerosis**➔ May cause ischemia to the kidneys.

C-**Pyelonephritis**: Inflammation in the parenchyma/interstitial tissue and **tubules** of the kidney. This disease has both acute and chronic forms.

- These lesions lead to renal failure, **which is considered as the second cause of death in diabetics (after M.I).**

- **All of these manifestations indicate that the kidneys are the main target of diabetes.**

- **Clinical manifestations of diabetic nephropathy**:

  ➔Diabetic nephropathy is considered as the leading cause of end-stage renal disease in the United States.

  ➔The earliest manifestation of diabetic nephropathy is the appearance of small amounts of albumin in urine (more than 30 and less than 300mg/day)➔**Microalbuminuria.**

  ➔**This is caused as a result of thickening of the glomerular basement membrane of capillaries leading to leakage of plasma proteins (including albumin).**

  ➔ Without specific interventions, approximately 80% of patients with type 1 DM and 20-40% of patients with type 2 DM will develop overt nephropathy.

  ➔Overt nephropathy is not only caused by thickening of the glomerular basement membrane, but also other diseases.

➔Manifestations of overt nephropathy include **macroalbuminuria** (excretion of more than 300mg/dl in the urine per day).

➔Overt nephropathy develops over 10 to 20 years, usually accompanied by hypertension.

➔ By 20 years after diagnosis, more than 75% of patients with type 1 diabetes and 20% of patients with type 2 DM with overt nephropathy will develop end-stage renal disease necessitating dialysis or renal transplantation.

3-Ocular Complications of Diabetes: (43:48)

➔ Might lead to visual impairment and blindness.

➔Blindness is considered one of the feared consequences of long-standing DM.

➔**DM currently is the fourth leading cause of acquired blindness in the United States**.

➔Retinopathy, the most common pattern, consists of changes that are considered by many ophthalmologists to be virtually diagnostic of the disease (these changes are specific for diabetics).

➔Retinopathy changes include **proliferative retinopathy** and **non-proliferative** retinopathy.

➔**Proliferative retinopathy** is characterized by new vascularization of retina, these vessels might contribute to **fibrosis** leading to blindness.

➔About 60% to 80% of patients develop a form of diabetic retinopathy approximately 15 to 20 years after diagnosis.

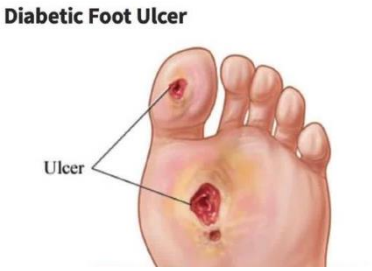
➔Diabetic patients also have an increased propensity for **glaucoma and cataract formation.**

4-Diabetic Neuropathy: (45:54)

We have three patterns in which neuropathy develops:

➔The most frequent pattern of involvement is that of bilateral, peripheral, symmetric neuropathy of the lower extremities affecting motor and sensory nerves (mainly sensory).
***Therefore some diabetic patients might not feel objects while they are walking. So, if a foreign body were to enter their leg due to trauma, this may cause ulceration there.

➔Autonomic neuropathy produces disturbances in bowel and bladder function and sometimes sexual impotence.



➔ Mononeuropathy, which may manifest as sudden foot drop or wrist-drop or isolated cranial nerve palsies. (defect in function of cranial nerves)

➔The neurologic changes may be the result of microangiopathy and increased permeability of capillaries that supply the nerves, as well as direct axonal damage.

- **Glycemic control**: How to assess if there is glycemic control after therapy of Diabetes Mellitus?

  ➔Glycemic control is assessed clinically by measuring the percentage of glycosylated hemoglobin known as HbA1C which is formed by nonenzymatic addition of glucose to hemoglobin in red blood cells.

  ➔Unlike blood glucose levels, HbA1C is a measure of glycemic control over a long period of time (2-3 months) unaffected by day to day variation.

  ➔The recommendation is to maintain HbA1C at less than 7% to reduce the risk for long term complications

THE END