



The Endocrine System



Sheet

Slide

Handout

Number:

4

Subject:

Parathyroid and pancreas

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Salam everyone 😊

In this lecture we will talk about the **Parathyroid gland** and the endocrine **Pancreas**.

Parathyroid gland:

[Hyperparathyroidism]

- Tumors of Parathyroid gland are **functional** tumors unlike those of the thyroid gland; as mentioned in the last lecture: 99% of thyroid tumors are **non-functional**.
- Parathyroid hormones increase the calcium concentration in the blood; so people with hyperparathyroidism will have hypercalcemia so the diagnosis is made after noticing that.
- Clinically we have 3 types of hyperparathyroidism :
Primary, secondary, and less commonly, tertiary hyperparathyroidism. The first condition represents autonomous, spontaneous overproduction of PTH, while the latter two conditions typically occur as secondary phenomena in individuals with chronic renal insufficiency.

[1] Primary hyperparathyroidism:

Primary means that the disease starts in the parathyroid gland and it's only of the parathyroid gland; unlike the secondary and tertiary hyperparathyroidism which caused by another disease found in the body.

Primary hyperparathyroidism is very common, and it usually presents as an incidental finding of hypercalcemia. Most cases are caused by adenoma (benign tumor) .Patients usually they are **Asymptomatic**, there is a silent elevation of the calcium in the blood (silent hypercalcemia), in contrast to cancer (much more elevated calcium); cancer is symptomatic especially in neuromuscular system.

Remember: The differences between adenoma and hyperplasia:

adenoma is a tumor and there's a mutation, it is autonomous and persistent.

hyperplasia there's a factor causing the disease (some exogenous factor causing the proliferation) and it is reversible.

In primary hyperparathyroidism; 80% of the common cases are secondary to parathyroid adenoma (single gland), whereas 15% is secondary to hyperplasia (4 glands evolved).

Since there are 4 glands, the tumor (the adenoma) will be in one region and one of the glands is enlarged not all four. As for hyperplasia, it activates proliferation in all the 4 glands and all of them will be enlarged.

Note: It's rare to have primary hyperthyroidism caused by carcinoma (5% of cases), which causes dysfunction and hypercalcemia.

- 95% of the cases are sporadic, meaning that there's no family history or other symptoms, and the remnant 5% are familial and they have other tumors in the body, and we call this **multiple endocrine neoplasia (MEN)**.

Another rare disease called **Familial hypocalciuric hypercalcemia**, *a rare case of hyperparathyroidism*, and it is caused by a mutation in the calcium sensation in the parathyroid gland (calcium-sensing receptor gene), it doesn't sense the normal level of calcium in the blood, which leads to constitutive secretion of PTH. **So** the patient would end up with hypercalcemia and low calcium urine.

Pathogenesis:

As for **adenoma**, there are genetic mutations:

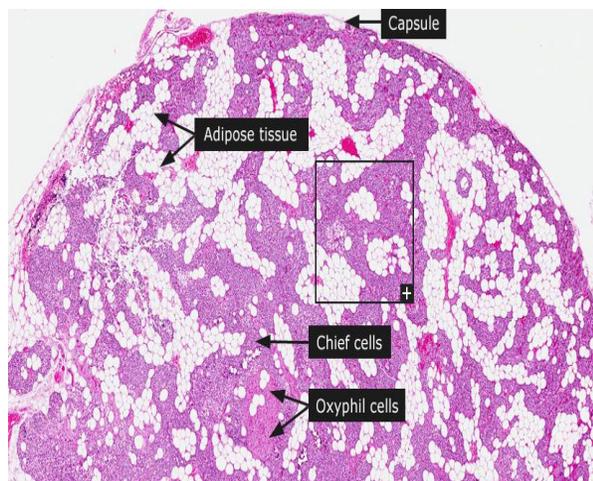
- 1- the most common one is parathyroid adenomatosis gene (**PRAD1**)
- 2- The second gene is **cyclin D1**, in adenoma, hyperplasia and carcinoma. Cyclin D1 is a protein involved in the cell cycle progression from **G1** till **S** ... all these checkpoints are regulated through cyclins that push them forward. If cyclin D1 is mutated; it becomes more powerful and active so the cells keep proliferating, and it is not specific in parathyroid adenoma its occasion in other human tumors like; lymphoma and liver cancer but in the parathyroid it is always there.
- 3- Multiple Endocrine Neoplasia gene (**MEN1**), if the gene is mutant; it causes tumors in the parathyroid gland. MEN is (**tumor suppressor**) gene; so if it is mutant the tumors can evolve.

Morphology (macro- and microscopic):

For the gross in macroscopic morphology, the **weight** of the parathyroid gland is a major concern.

In adenoma there is single enlarged gland from (0.5-5) g, this is the expected weight for adenoma, and the rest three glands are atrophic as a result of feedback inhibition.

For hyperplasia the enlargement is for multiple glands not just one, usually the four glands together don't exceed 1g in weight. In carcinoma the usual weight is > 5g and there is invasion (spread into the surrounding tissue), metastasis and an adherent mass in the neck. Parathyroid glands are hardly seen in normal status and their weight (all together) doesn't exceed 0.2g, however in these cases as you can see they are much heavier and larger.



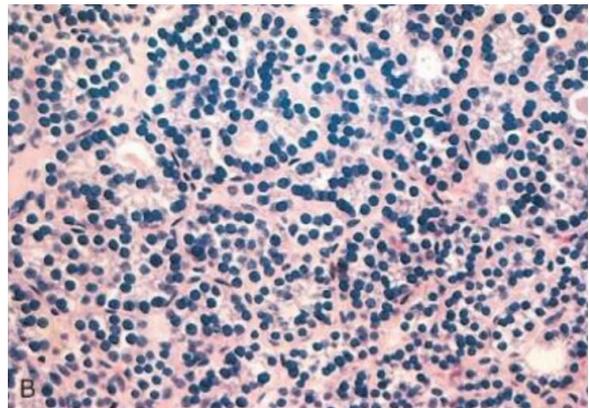
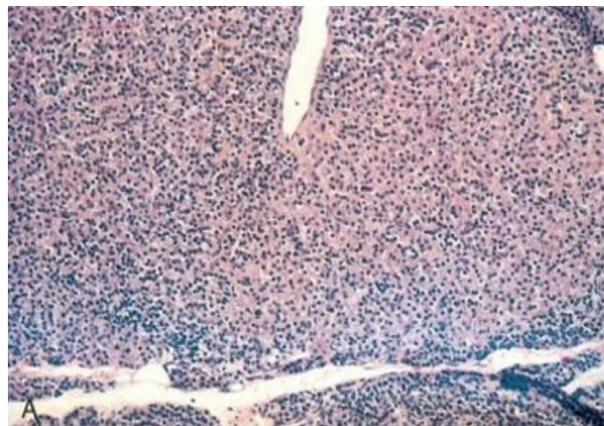
The normal histology of the parathyroid:

We notice chief cells and fat cells, in older ages the amount of fat increases at the expense of the endocrine cells.

Adenoma:

There is proliferation; composed predominantly of chief cell. And much less fat is seen.

In the figure A we can recognize a dense fibrous capsule separate the adenoma tissue from the residual gland below which is a helpful internal control.



Normally, cells of The endocrine system may show **atypia** (structural abnormalities), which is a sign of malignancy in epithelial tumor, so some element of atypia is normally present in the endocrine system; some cells are larger than the other cells and this is due to variation in the function and number of the receptors, some cells appear larger than the other and this **doesn't** mean malignant behavior. In malignancy the definite thing is to see invasion or distant metastasis so even the adenoma sometimes we see atypia in the cells.

[2]Secondary hyperparathyroidism:

It appears when there's a long standing hypocalcemia that will activate the parathyroid gland to proliferate and compensate the hypocalcemia. The most common cause of secondary hyperparathyroidism and hypocalcemia is the **chronic renal failure**.

The mechanism of hypocalcemia it is much unknown but the theory is that patients with renal failure don't excrete phosphate so the hyperphosphatemia will suppress the calcium level. Also, vitamin D activation occurs in the kidneys so when there's a renal failure there's no much activated vitamin D and this would decrease the absorption of calcium from the GI system resulting in hypocalcemia.

Morphology:

Enlargement of the 4 glands, in some cases even after the correction of the renal failure for the patient, the glands keep secreting calcium and parathyroid hormone (autonomous hypercalcemia) even if calcium is back to normal this case is called the **Tertiary hyperparathyroidism [3]**.

[Hypoparathyroidism]:

It is a rare disease; so destruction of the 4 glands is needed to develop hypoparathyroidism, most commonly by **surgical removal of the thyroid** and sometimes by **congenital absences** which could occur in many organ, **autoimmune disease** and severe **infection** in the neck will destroy the parathyroid gland.

The patients will show hypocalcemia and it is symptomatic; symptoms appear in the neuromuscular system as abnormal function.

Endocrine pancreas:

We will talk about diabetes because it is the most common and **most** important disease in medicine.

Diabetes mellitus is a group of disease that shares the same phenomena which is ***persistent hyperglycemia***. Hyperglycemia means increased glucose concentration in the blood and it is a chronic, persistent and lifelong disease.

Why do we get hyperglycemia?

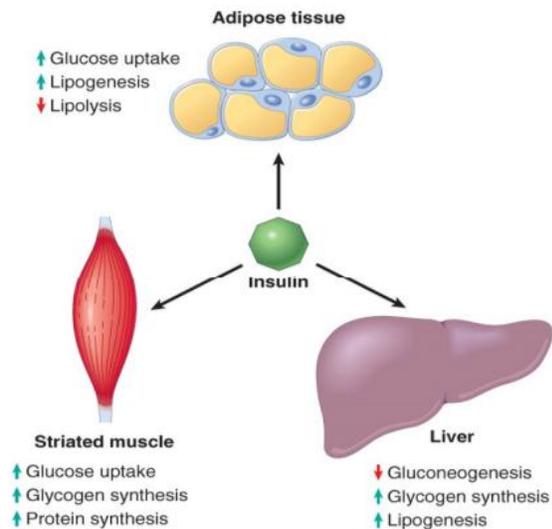
It is either due the absence or decreased secretion of insulin from the pancreas, **OR** there is a resistance in the peripheral tissues to insulin function. So in both conditions the patient would have increased glucose in the blood. Glucose doesn't enter the tissue it stays in the blood so the patient will have **diabetes**. Diabetes is an important disease because it is common and patients will have a lot of morbidity; quality of life is poor because it damages any organ in the body. It is the most common cause of end-stage renal failure, adult-onset blindness and non-traumatic lower limb amputations.

Some points regarding insulin:

- It's an **anabolic** hormone so it always build things; it shift the glucose into the tissue, As for the fat cells; it increases the uptake and the synthesis of fat molecules so it's a lipogenic factor and it inhibits lipolysis process (breaking down of fatty acids).

Striated muscle (skeleton muscles) & cardiac muscle also take glucose and they synthesis proteins and glycogen as well as the liver that also synthesis glycogen after the uptake and inhibit the glycogenolysis of glucose **SO** it is insulin is **anabolic** hormone.

- Reduces gluconeogenesis.
- Promotes amino acid uptake into muscles & protein synthesis, inhibit degradation.
- Promote DNA synthesis, cell growth & differentiation.
- In fasting state, insulin is low.



NOTE: There are other tissues that do not need insulin in order to get the glucose inside such as:

- Brain
- nerves
- blood vessels

Types of diabetes:

Type 1 diabetes Mellitus is characterized by the following:

- 1- Destruction of the B-cells that secrete insulin in the pancreas. Most commonly there's autoimmune disease (**insulinitis**) .
- 2-Clinically the patients are young when they develop this disease.
- 3- This type of disease is rare; typically 10% of all cases, unlike type 2 diabetes.
- 4- The period between the beginning of the disease and the appearance of the clinical symptoms is **short**.

Pathogenesis

• Break in tolerance to β -cells or insulin

-Autoimmune disease:

CD4-T lymphocytes, secrete $\text{INF-}\gamma$ to **activate** CD8-Tlymphocytes & macrophages (secrete IL-1, TNF) that damage β -cells, also **activate** B-lymphocytes to produce auto antibodies against insulin or β -cells.

-Causes:

1. Genetic predisposition:

* Human lymphocyte antigens (HLA) :

[HLA-DR3, HLA-DR4]

*T-cell inhibitory receptor CTLA-4: an antigen presents in the T cells and people who carry this one have a more chance to have diabetes.

2. Viral infection; most common viruses are :

*Coxsackie b virus.

*Cytomegalovirus.

Type II diabetes Mellitus is characterized by the following:

1-Type 2 is more common in adults.

2-it is much more common than type one 80-90% of cases.

3- The patients usually have normal secretion of insulin but they develop resistance to the function; the peripheral tissues don't respond to insulin.

In normal situation in the endocrine system, resistance and non-responsiveness to hormones induce by increasing the secretion of the hormone .In these patients, the pancreas will secrete more insulin but quickly it develops failure. So the patients will have the peripheral resistance and a relative deficiency secretion; There is secretion but it is not enough so the insulin is there but it is not functional.

4- The onset of these patients from the peripheral resistance to the development of diabetes is a long time it takes years and sometimes decades; as the resistance could occur within 20s of age but the patient after 20 to 40 years would be able to see the result of diabetes so it is a very long process.

Pathogenesis:

-Most complicated, the immune system is totally normal **but** they still have genetic predisposition (this genes are unknown)

-Most patients have a family history.

-The environmental factors play an important role in this type; specially: **obesity** and the **lifestyle (sedentary lifestyle)**

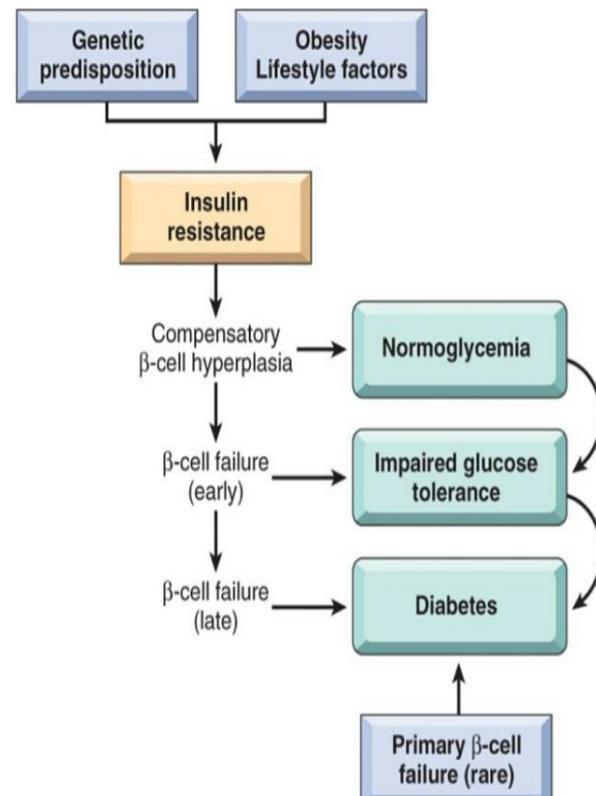
-So a **mix** of genetic & environmental factor will end up with **insulin resistance** in liver, adipose and skeleton muscle.

-Once we have resistance the cells will response by proliferating in the B-cells and secretion of more insulin.

-Patient in the early phase they are Asymptomatic (glucose level is normal)

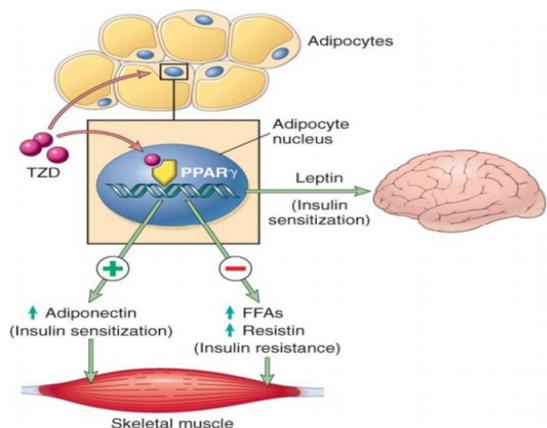
but then the process will go on and with time the pancreas will fail so we will have relative deficiency (insulin is less than normal) so the patient will develop what's called "impaired glucose tolerance" which is a pre-diabetic state of hyperglycemia.

-After the level of impaired glucose tolerance the patient will have the real diabetes and the symptoms start to appear.



BUT WHY DO WE HAVE RESISTANCE??

Obese patients have more fat cells, fat cells can be considered as an endocrine organ, normally fat cells produce **Resistin** and **free fatty acids** and **Adiponectin** they are important in the metabolism process.



- Resistin and free fatty acids normally decrease the response to insulin and Adiponectin (insulin sensitizer) increases the response of insulin in fatty tissue ...

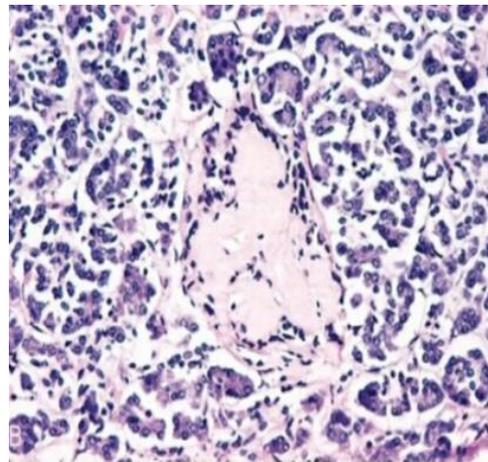
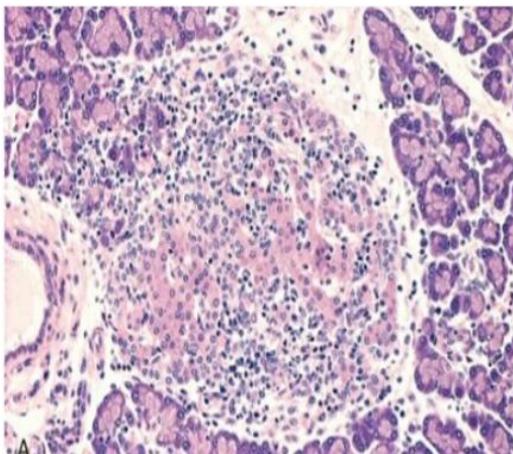
SO obese people will have an increase in the number of Resistin and FFAs and

decrease of Adiponectin so they will have a resistance to the insulin (insulin is present but they cannot shift the glucose into the cell).

-Also the FFAs are harmful to the pancreas; they affect the function and also do physical destruction to the B-cells but it isn't prominent as in type 1.

NOTE: The pancreatic cells of this type of diabetes will appear under the microscope with a deposition of amyloid; any degenerative disease molecules that present abnormally, in this case amyloid is the abnormal molecule so give **amyloidosis**.

Morphology:



#On the left this is **type 1 DM**, you can see in the rim the islet cells which is normal and in the middle we have a large area of plasma cells and lymphocytes cells and **destroyed** islet cells.

#On the right this is **type 2 DM**, you see amorphous material (a: without, morph: morphology, shape) which is the amyloid and we don't have lymphocytes.

-The stain of the amyloid is Congo Red so the tissue in the right is positive but on the left is negative.

Monogenic DM:

Monogenic is another clinical term for diabetes, which means that there is a **single** gene that is mutant and causes diabetes. Monogenic means there's **single mutation** leading to a deficiency in **one enzyme** producing a **disease**, this is very rare. You won't be able to discover this unless you do a genetic test but this is not performed routinely. Some people have diabetes due to single gene mutation and this is what we call monogenic diabetes. This gene is either in the synthesis of insulin or in the cellular cascade when the signal transduction works in the target cell. The enzyme maybe work in the synthesis of insulin or in its action inside the cell **so** the patient will end up with diabetes.

- The gene related to this diabetes: there are multiple genes (6 categories), we only have to know the name which is **MODY gene** (monogenic diabetes genes).

Other common causes for diabetes mellitus (rare):

- **Loss of pancreatic tissue**: there is a destruction of the cells it like the type 1 diabetes but it is not autoimmune, it happens with pancreatic carcinoma or fibrosis and these patients die because of the cancer.
- **Increased hormones that antagonize insulin**, insulin is anabolic hormone and it is strong, it is a muscular hormone, it has **[4] antagonist** make a balance with it ; if any one of these antagonist increase the insulin will be affected and decrease which cause hyperglycemia.

These antagonist are :

-**GH** : if it increase it will cause Gigantism and Acromegaly, those patients will have hyperglycemia .

-**Cortisol**: high level of it causes Cushing's syndrome which combine with hyperglycemia.

If you take cortisol as a treatment such as a patient suffering from rheumatoid arthritis or someone that has Asthma, they always get their glucose levels checked because the glucose levels for them could increase.

-**Glucagon**: hormone secreted by pancreas ...in case of **glucagonoma** there is excessive synthesis of glucose so there will be hyperglycemia so diabetes.

-**Thyroxine**: is another hormone that causes hyperglycemia in the case of hyperthyroidism.

-**Epinephrine**: can be classified as a hormone and it can cause hyperglycemia.

- **Viral infection**: it could cause direct damage or on the antigen CD on the B-cells (CMV, Coxsackie B that cause pancreatitis).
- **There are also some drugs that cause hyperglycemia such as B-agonist** these drugs dilate the bronchus and cause muscle relaxation. Asthma patients take this drug as an inhaler and it can also cause hyperglycemia.
- **There are also syndromes like: (Down, Klinefelter, and Turner) syndrome** which is where the patient has multiple systemic of disease including diabetes.
- **Gestational diabetes** is a clinical term which means high blood glucose level during **pregnancy**; the woman usually is in impaired tolerance phase or in resistance phase but because the excessive demand of insulin; hyperglycemia will happen but after birth delivery it will go.

What is The effect of hyperglycemia?

Hyperglycemia, if long standing, will cause damage to any organ in the body and all systems. At the cellular level it is important to know what happens:

[1] non-enzymatic glycosylation of proteins:

- Glucose and sugars are sticky, they stick to proteins and this doesn't need an enzyme so it's called non-enzymatic glycosylation of protein in the blood and in the blood vessels e.g. hemoglobin A1C. There is hemoglobin A meaning it's adult it is the most common type there is other types but the most common type is hemoglobin A. Glucose would stick to the hemoglobin A so it's called hemoglobin A1C and C means glycated(it is sweet). It is of clinical significance to measure and quantify hemoglobin A1C (السكر التراكمي). For diabetic people it is higher than the normal levels.

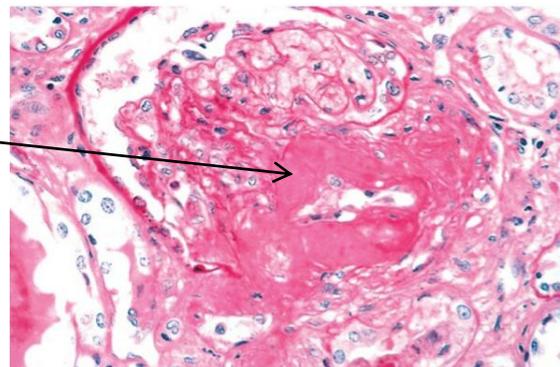
- **Blood vessels:** hyperglycemia affects the collagen in the blood vessels, they become sticky, and they stick to each other make cross linking and change the molecule that are secreted in the blood.
 - The most important is the **lipoproteins:** they adhere to the blood vessels and at the end they will develop atherosclerosis.

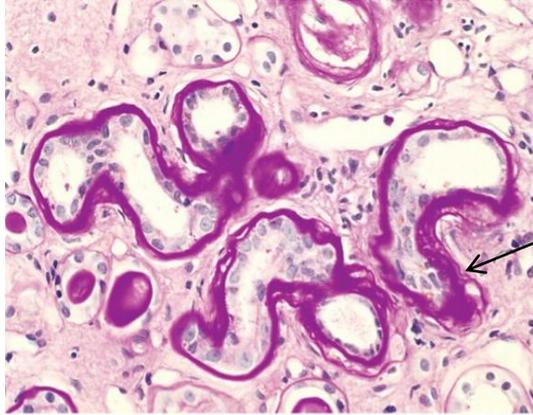
- **Note:** diabetic patient will have other diseases with diabetes commonly atherosclerosis and hypertension.

- **The kidneys:** it will cause renal failure, the same concept for glucose it will affect the basement membrane in the glomeruli .Always after filtration we have reabsorption; and because the protein in this case is albumin... Albumin will stick on the basement membrane and then cause changes in morphology and function; this will activate the endothelium which will secrete of cytokines; and then the cytokine will make a minimal inflammation and proliferation of stromal cells.The fibroblast is like the smooth muscles that is why the blood vessels become thick, proliferation of smooth muscles and fibroblast cause hypertension.

There will be a proliferation of mesangial cells of glomerulus and because of that the glomerulus become filled with cells and materials [basement membrane and the mesangial cells] and then its shape and function will change, and with time we will have a **fibrosis**.

This is a glomerulus; we have blood vessels in the middle and the lumen inside, the blood vessels is very thick because of the deposition of the materials.

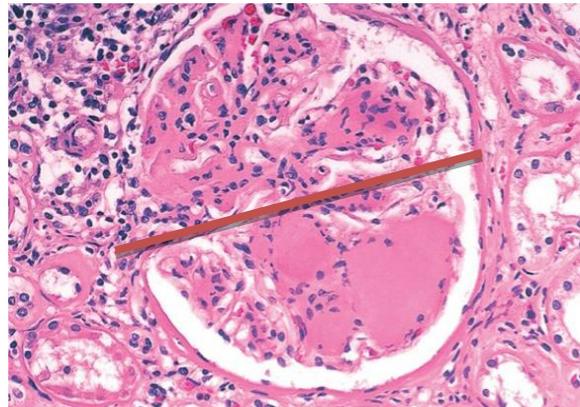




This figure presents kidney tubules, look at the walls(basement membrane)

They are very thick so the function is impaired...normal basement membrane appear as line.

This is another picture of the glomerulus: in the upper half there is a proliferation of the mesangial cells (there number is more than normal) ... and in the lower half there is deposition of material and fibrosis; because of that the kidney stops working normally.



The second and the third mechanism are taking place in the tissues that don't need insulin in there metabolism as **Nerves, the lens and the kidneys.**

[2] Activation of protein C:

-in the case of hyperglycemia, a much more amount of glucose enter into the cells (passive movement) so this will have increase glucose inside the cytoplasm; this increase in glucose will induce metabolic changes inside the cells ... **HOW?**

Firstly, it will activate **protein c** → activation to transforming growth factor (TGF-β) which is an angiogenic molecule causes proliferation of the blood vessels.

-This process is important in the eye (retina) ; patient with diabetes usually visit the ophthalmologist ;because as we said before that diabetes is one of the most common cause of blindness which secondary to this process..SO by this process

the patient will have a lot of vessels in the retina ...when you examine them you will see an abnormal vessels are growing there ... these vessels are physical barrier so they cause blindness and also if they bleed and bleeding in the retina is very harmful and cause blindness.

[3] Intracellular hyperglycemia with disturbance in polyol pathways

-This mechanism is concerned of increasing the **sorbitol** in cytoplasm.

-**Sorbitol** is a byproduct of the glucose (metabolism process; sorbitol & fructose)

-It is a potent osmotic molecule, if it exists; it will drag fluid inside the cell so the cells become swollen and the function will be disturbed.

- The second thing is that sorbitol will deplete the normal antioxidants, as we know cells create harmful molecules called **oxidants** during metabolism. So any cell in the body contains antioxidant to balance the oxidant molecules.

-The sorbitol causes depletion of antioxidants; it attaches to the antioxidants and neutralizes them. So during metabolism the oxidants levels of those cells will be higher than the normal and they cause harm to the cells that's why this causes damage in the nerves and loss of sensation for the patient. This is how diabetes causes damage to the tissues.

-The End.

وإنك إن لم تزدد على الحياة شيئاً ... تكن أنت زائداً عليها !