University of Jordan - Faculty of Medicine
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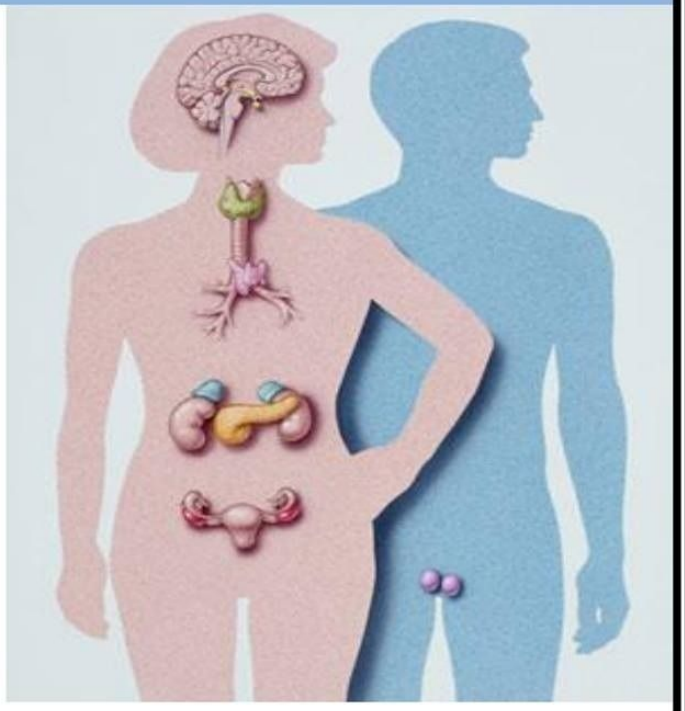
Medical Committee
The University of Jordan

Endocrine System



- [ ] Anatomy/Embryology/Histology
- [ ] Biochemistry
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Sheet #: **6**

Date:

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DIABETES MELLITUS

Diabetes Mellitus is a group of metabolic disorders sharing one feature which is hyperglycemia .(it's not a single disease)

- **Blood glucose levels normally are maintained (tightly regulated) in a very narrow range by insulin and glucagon , usually 70 to 120 mg/dL**.

Usually problems which deal with glucose levels in the blood are primarily related to insulin and rarely to glucagon .

Insulin function :

-Decreases blood glucose.

-Insulin Increase uptake of glucose by striated muscle and adipocytes .

-Insulin has anabolic effect on lipid, protein and glycogen.

-Insulin reduces production of glucose from liver.

* Each glucose molecule we take from our food is absorbed by one of several mechanisms and from different places 'kidney,intestines...'
* Mechanisms of absorbing glucose are passive diffusion , facilitated diffusion and active transport .

* Under normal conditions human body doesn't lose any glucose molecule .

* One of the mechanisms glucose enter certain types of cells is by insulin.

* Tissues which depend on insulin in transporting glucose are skeletal tissue " striated muscles" and adipose tissue.

* Insulin is the most potent anabolic hormone in our bodies , it is anabolic to every thing ; their anabolic activity results in the production of glycogen , adipose tissue and proteins

* Insulin decreases destruction of lipids "lipolysis" , glycogen " glycogenolysis ;so glycogen is not converted to glucose and glucose will not go to blood " and proteins .

DM is a problem which causes increase in the glucose level in the blood , but not every person with high glucose level has diabetes .

Diabetes Mellitus is diagnosed by any one of three criteria "presence of one is enough;either #1 or #2 or #3"

1. A **random** blood glucose concentration of 200 mg/dL or higher, with classical signs and symptoms "which we will talk about later on".
2. A **fasting glucose** concentration of 126 mg/dL or higher on more than one occasion "at least 2 times".
3. An **abnormal oral glucose tolerance test (OGTT),** in which the glucose levels is 200 mg/dL or higher , you give the patient 75g of glucose and after 2 hours we measure the glucose in the blood . Usually we use this test with pregnant women to investigate gestational diabetes .

In practice, mainly we do the fasting test.

*People who are in between the normal and abnormal glucose levels (120-126) mg/dL are in a state called pre-diabetes or impaired glucose intolerance .

*Persons with pre-diabetes have an elevated risk for development of frank diabetes.

Classification of DM :

- **Type 1**

Absolute insulin deficiency; due to autoimmune destruction of the islets of Langerhans.

- **Type 2**

- Relative insulin deficiency, insulin is normal or near normal but in these people their Peripheral tissues "skeletal muscles and adipocytes" do not respond to insulin ,insulin doesn't bind to its receptors ;so glucose is not taken "Peripheral resistance to insulin"
- If the islets are normal, they will secrete more insulin to overcome this problem , so we need another factor in addition to the resistance to have a diabetes , which is reduction in the production of the insulin by impairment of islets of langerhans "beta cell"

,which is called impaired over production of insulin which causes relative insulin deficiency .
- Resistance to insulin and inadequate compensatory response of insulin secretion.
- Usually this type is related to obesity.

Other rare causes “Type 3" ·

It mainly causes early onset of diabetes.

Several genetic mutations may cause this type of diabetes , we don’t need to know all of them ; what we need to know that there is subtypes of diabetes neither type 1 nor type 2 related mostly to genetic defects.

Here are the main causes and classes of this type :

1)Genetic defects of beta cell function.

- One of these defects is "**maturity onset diabetes of the young= MODY**" due to certain mutations that affect insulin production ,so we expect to see this type in young age , these defects may be in insulin gene or in proinsulin conversion.

2)Genetic defects in insulin action , insulin doesn’t act on peripheral tissues “not acquired problem like type 2” , Insulin cant bind to its receptors and cannot do its action, mainly this point deal with insulin receptors (this subtype is not because of an acquired problem like type 2, its mainly because of Genetic defects).

3)Gestational diabetes “The most impotant subtype of diabetes type 3”

This type is associated with pregnant ladies o.O

4)exocrine pancreatic defects, when these defects are sever enough to destroy the endocrine part, so we can see diabetes in patients with chronic pancreatitis, pancreatectomy, neoplasia(pancreatic tumors)..etc

5)Endocrinpathies ‘complications related to endocrine problems’
Acromegaly , cushing syndrome, pheochromocytoma all these complications can produce symptoms like Diabetes .

6)Certian infections '**very rare'** like CMV, coxackievirus B , congenital rubella.

7) Some drugs may produce this type of diabetes like **steroidal drugs**

- Vast majority of diabetes patients suffer from type 2 (80%-90%) .Type 1 (10%),and Type 3 (much less than 10%) .

TYPE 1 Diabetes :-

- It accounts for 10% of all cases .
- Is an autoimmune disease which mean we have antibodies against the enzymes that synthesize insulin>> destructing Pancreatic B cells leading to an absolute deficiency of insulin .
- Most commonly develops in childhood and symptoms start to appear at puberty, patients need insulin replacement therapy ; without insulin they develop complications.
- The classic manifestations and symptoms of the disease occur late in its course , after 90% of the beta cells have been destroyed.

-There is genetic predisposition in this type, all autoimmune diseases have genetic predisposition and can be associated with other autoimmune diseases .
*some people think there is an effect of viral infection in this type but nothing is improved till now !!

Pathogenesis:- autoimmune:""الدكتورة ماركزت علي بهم

a. Defective deletion of self-reactive T cells in the thymus,
    - Defects in the functions of regulatory T cells
    - Auto-antibodies against B cell antigens, including insulin and enzyme glutamic acid decarboxylase, are detected in the blood of 70% to 80% of patients

Type 2 diabetes :

Accounts for 80% to 90% of cases

- Caused by a **combination** of "both"

a. Peripheral resistance to insulin action and

- An inadequate compensation response by the islets of langerhans .

- **Obesity can provide the essential causes to Diabetes type 2** ;obesity can cause Peripheral resistance and inadequate compensation response.

Insulin resistance: :

- Is defined as the failure of target tissues to respond normally to insulin by certain mechanisms , prevention of insulin from binding to its receptors and therefore no action.
  - It leads to decrease the uptake of glucose into muscle cells, adipose tissue and increase glycolysis in the liver and other actions …

The cause of insulin resistance is obesity(any degree of increased fat will cause , to some extent, insulin resistance);

Visceral fat plays an important role in insulin resistance , always it causes a degree of insulin resistance , maybe it is not enough to develop full resistance but its effect can't be hidden .

- The risk of diabetes increases as the body mass index increases, suggesting a dose-response relationship between body fat and insulin resistance.

Obesity and insulin resistance:

A. Role of excess free fatty acids (FFAs):

Obese people has an increased level of FFA , these FFA deposits and become Triglycerides (TGs) , these TGs block insulin receptors , therefore reduce the response of these tissues to insulin .

-Intracellular triglycerides are potent inhibitors of insulin signaling and result in an acquired insulin resistance .

b. ***Role of inflammation*:**

FFA increases the production of cytokines (specially interlukin 1 beta "IL-1β")

IL-1β causes insulin resistance and beta cells dysfunction .

- Excess FFAs within macrophages and beta cells can engage the *inflammasome*, leading to secretion of the IL-1β which mediates secretion of additional cytokines from macrophages, that are released into the circulation and act on the major sites of insulin action to promote insulin resistance.

C. Role of adipokines: Adipose tissue release *adipokines* e;g IL-1β which promote peripheral insulin resistance

Adipokines = cytokines produced by adipose tissue .

#There are 3 mechanisms by which obesity causes peripheral resistance ;FFA converted to TGs (which "TGs" block insulin receptors),FFA increases cytokines (specially "IL-1β") and adipokines produced by adipocytes.

Beta cell dysfunction

Obesity itself affects Beta cells function , so they won't be able to produce the needed extra amounts of insulin needed due to the resistance .

- Cause: multi-factorial and overlap with those related to peripheral resistance.

Cytokines and FFA will affect Beta cells and produce an inflammatory damage , this inflammatory damage means Beta cells won't be able to produce extra amounts of insulin and with time their normal production will decrease because of the destruction >> in late stages absolute deficiency .

In early stages of diabetes type 2 you can treat the patient by changing their lifestyle < the first line of treatment is (exercise – diet) << lose of weight

Lose of weight << reduction of FFA << No cytokines << No insulin resistance << every thing will go back to normal

But in late stages in which Beta cells are destructed we give insulin supplements even if weight is reduced ; because islets were destructed .

Another way by which islets were destructed is by amylin protein which is secreted by the β- cells and its abnormal aggregation results in amyloid that replaces the islets(the islets will be lostabsolute insulin deficiency).

Clinical features of DM:

Polyuria:

Normally glucose is not lost in urine because glucose is essential to our body as the main source of energy and in order not to lose glucose in urine there are several mechanism for the reabsorption of glucose such as; passive diffusion, active diffusion and facilitated diffusion but in hyperglycemia the threshold is too high for the kidney to handle so glucose will get out with urine (glucouria). Glucose increases the osmolarity in urine, so by osmosis water gets

out, the patient lose more water by urination. Also thirst centers in brain are stimulated, and then the patient will have **polydipsia.**

Polyphagia: they eat a lot but they lose weight because the most potent anabolic hormone (insulin) is lost, anything they eat is catabolized.

Complications of diabetes:

All the complications are related to hyperglycemia and the most important complications those which are associated with long- term hyperglycemia.
Doctors control the blood glucose level of diabetic patients so they can live a normal life, but if glucose goes high this will cause several problems, the main 4 sites are:

1-blood vessels
2- kidneys
3- eyes
4- central nervous system (CNS)

How does glucose affect these organs?
The main idea is when glucose is high it produces certain chemical

compounds which are toxic and can cause destruction to blood vessels and other tissues.

These compounds are:

1--advanced glycation end products (AGEs)
when glucose is high it attaches to amino acid residues in proteins , and these attachment produces what we call (AGEs) which cause an injury to the blood vessels (mainly) and other organs which are supplied by blood vessels.
* the process of the attachment between glucose and amino acid happens normally in our bodies , but it is regulated in order not to cause a damage*

in diabetic patients this process is not regulated causing epithelial damage in blood vessels by:
1-releasing cytokines so inflammatory destruction will take place in the blood vessels.
2- Stimulating growth factors. As we know lumen in the body is important, when it is wide enough it facilitate the blood flow. But more growth in endothelial means we are increasing the epithelium and decreasing the lumen so decreasing the blood to the tissue
3- producing oxygen free radicals which damages blood vessels.
4- Increasing coagulation which damages blood vessels and increases atherosclerosis.
So the net effect of AGEs is damaging vessel's wall of the eye, kidney, supplying the nervous system and all over the body.

2--**Increasing of glucose activates protein kinase C**, which will increase the synthesis of diacyelglycerol (DAG) which will cause the production of certain proangiogenic molecules.

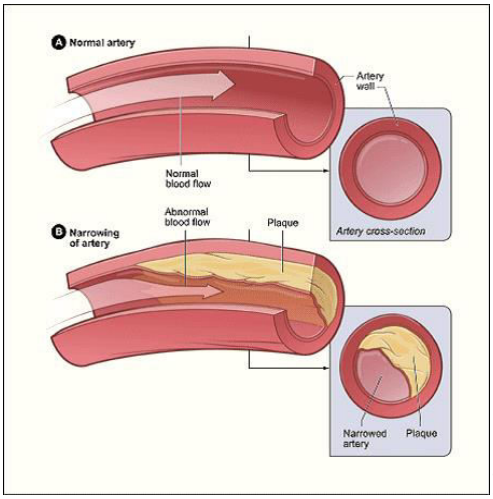
DAG affects blood vessels by:

1- increasing vascular endothelial growth factor (VEGF), which will cause growth of endothelial cells which result in the closure of blood vessels.
2- Stimulating transforming growth factor β, which deposits the extracellular matrix .This, is important in kidney specifically.

** keep in your mind the main idea: when glucose increases, it produces certain materials which cause damage in blood vessels supplying many organs**

3—**disturbances in polyol pathway**
anything ends with (-ol) means alcohol .certain tissue gets glucose without the need of insulin like in brain, RBCs, kidney and blood vessels. So when glucose is high it is converted to fructose, a step happened in this conversion before reaching the fructose. As intermediate compound, sorbitol -which is one of the polyols -is produced. The production of sorbitol needs NADPH, so NADPH is depleted in neurons (for example).
NADPH is important because certain oxygen derived free radicals in our bodies that needs to be detoxified in the presence of NADPH
so depleted NADPH will cause accumulation of toxics in the cells will cause damage by oxidation activity, for example: axonal damage (damage in neurons) causing neuropathy.

Morphology and clinical manifestations of complications:



1-**In large blood vessels causing atherosclerosis**: when a large vessel gets partially blocked by accumulation of fats, cholesterol and inflammatory cells causing infarction. Myocardial Infarction is the leading cause of death in diabetic patients.

* The mechanism is mentioned above (glucose producing toxins which damage blood vessels….)


2-**hyaline arteriolosclerosis**

it happens in diabetes and hypertension, blood vessel has hyaline section (eosinophilic material around the blood vessel causing leaky and damage to the blood vessel wall)

3-**diabetic microangopathy**

small vessels and capillaries are affected, basement membrane thickening in capillaries of kidney, skin, and retina.

*in diabetes:

large vessels affected >>>>> by atherosclerosis

smallvessels and capillaries affected >>>>> by microangopathy

Also there is neovascularization, by increasing in growth factor, so increasing vessels formation as a result the retina is affected and blindness will occur.

4- **Diabetic nephropathy**
diabetes affect the kidney specifically the glomerulous (the cappitaries which supplies the kidney), atherosclerosis happens in glomerulous so it becomes non functional and it can ends in chronic renal failure. Thicking of the basement membrane tubules takes place here

that is what you need to know here for now, further information about this topic will be discussed in urogenetal system

5- **Pyelonephritis**
diabetes increases the infection and inflammation of the kidney also diabetes suppresses mildly the immune system and causing infections and inflammations

6- Neovascularization and they can have blindness
most common pattern of eye involvement is **retinopathy** (problem in the retina) and this occurs in 60-80% of patients if the disease last for 15-20 years.
Not all retinopathy cases end with blindness but all patients with diabetics after 15 to 20 years of the disease have retinopathy.

7- Diabetic neuropathy in which Neurons are affected by many ways:
-**peripheral symmetric neuropathy** ……"most common"
a problem in sensation of both legs and less likely in motor movement
so diabetic patients should be away from heat resources because if

they did they can burn themselves without sensing it. And should not trim his fingers in order not to harm him without sensing it

-**Autonomic neuropathy**
they can't control their bowel and bladder function, and they might have sexual impotence

-Mononeuropathy
one single nerve affected.

Usually neuropathy is related to **microangiopathy** affecting blood vessels that supply the nerves, or **direct axonal damage** (polyol pathway that we talked about it before).

Management of diabetes:
type 1 >>>>> by insulin
type 2 >>>>> starting by changing life style, then hypoglycemic drugs, and finally insulin if we reach point of no return

NOTES:

*Usually diabetes is accompanied by hypertension
* when atherosclerosis happens in blood vessels that supplies the limps, so less blood reaching there , ischemia and gangrenous takes place , infections can happens sowe treat the limps with amputation because the limp will become non functional and source of infection

This sheet is dedicated to قرأيه مياذ ادي ,

(Qasemshajrawi, , Ismail KokashHussamAtieh, Ahmad Abushehab) Jama3et el Yarmouk ", Ali Khresat , MuhannadHaddadin , Abu zghoul ,Abu shehab, Omar Hamdan,qusai shareif ,RakanRadi,Jari elzene5 Abul 3abed and finally our beloved LAJNEH specially KhaledSmadi<3

عمّي وه لا...