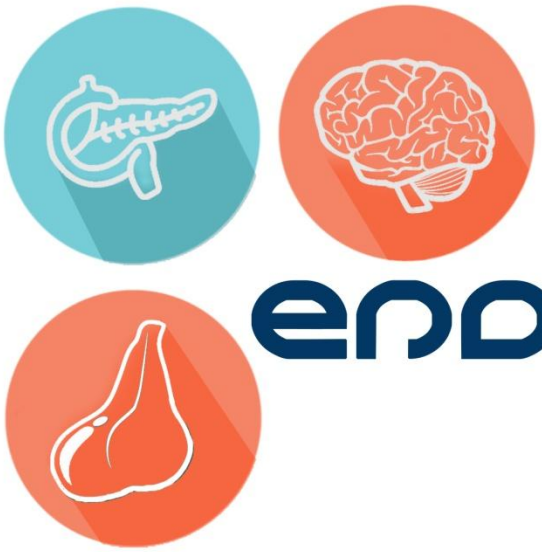

endocrine system

Pharmacology

Sheet Slide

number	7
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Diabetes mellitus

◊In this lecture we will continue taking about the management of type2 DM

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③Biguanides

*The most important drug in this group is Metformin

➡MOA:

1) reduce gluconeogenesis in liver and kidneys.

2) Decrease hyperlipedimia

3) Decrease glucose absorption from the intestine

4) Keep the beta cells alive

5) reduce plasma glucagon levels .

➡Side effects:

*Metformin may cause gastrointestinal disturbances such as diarrhea in the first 2 weeks of administration in 20% of patients, even though after the 2 weeks only 7% of the patients will still have the side effects.

*To overcome this problem; we use something called **Dose Escalation,** that means ; instead of giving the patient the full dose (in this case, it is1700 or 2000 mg), we start with low dose (500mg for example), and then rise the dose to reach the desirable dose.

➡Contraindicated cases:

1) In patients with Renal diseases with glomerular filtration rate below 30 ml/minute ; because of the high susbectibilty to those patients to develop lactic acidosis (which is a very rare side effect in healthy patients).

2) Pregnant females: in the clinical practice, some doctors using it but off-label (unapproved use). The drug is not teratogenic but it is contraindicated because it is risky for the fetus to have fluctuations in glucose concentrations therefore the drug of choice in pregnancy is insulin.

➡It has NO kidney toxicity effect.

➡Ideal for obese patients, it can cause some weight loss on this group of people only. But in overweight patients it does not cause weight loss .

➡Metformin is the drug of choice in the case of DMT2; so in all cases we start with it, with time the kidney function will decline with age, and we should use another drugs such as Meglanitide.

- Metformin does not cause hypoglycemia, because the glycolysis activity in the body will still moderate, even after using the drug.
- Metformin reduces the A1C by 1.5 .

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④Glitazones

➡they take a time to function as well as to finish; because they work intracellular (on the gene expression).

➡MOA:

*these drugs affect the gene expression of PPARs (a group of nuclear receptors; PPARs alpha, PPARs beta and PPARs gamma)

*These receptors control many other genes expression; that control the homeostasis of lipids and carbohydrates.

*The drugs **modulate** the expression of the PPARs, which result in increase the sensitivity of insulin; so these drugs called insulin-sensitizers.

➡They don't produce Hypoglycemia.

➡These drugs have many issues such as bladder cancer, so they are restricted from many countries.

➡There are new drugs of this group that act on PPARs beta and gamma, and overcome these issues.

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⑤Alpha-Glycosidase inhibitors (Acarbose and Miglitol)

➡They cause delay of the glucose absorption; but they are not really effective.

➡They can cause flatulence, diarrhea, chronic ulceration and bowl disorder

All these 5 groups are old generation drugs.

We will start taking about the new generation drugs:

①GLP-1 affecting drugs

*before we start talking about these drugs we will discuss what GLP-1 is?!

*there is a group of hormones secreted from the GIT called incretins, and one of them is GLP-1.

*GLP-1 secreted in response to meal from the L-cells in the intestine; and cause suppression to the glucagon secretion ,stimulate glucose dependent insulin secretion , slow gastric emptying, reduce food intake and maintain beta cells efficacy and increase beta cell mass.

*In DM we need GLP-1 active for longer time; so we will increase its half life by two ways:

A) Inhibition of the GLP-1 metabolizer (Dipeptidyl-peptidase), by a drug called **Januvia (the trade name)**

➡ All the generic names for the drugs ends with Glipten (know that about names and enough)

➡MOA (These drugs will fix two broken organs in the patients):

1) Suppression of glucagon secretion

2) Enhance insulin and amylin secretion

➡very little side effects such as runny nose and upper respiratory infection

➡They are taken with metformin; because they don't cause significant decrease in the A1C (accumulative glucose); this mix drug is called

Mit-januvia

➡So, the rule of Glipten drugs is to keep the pancreatic cells alive.

B) GLP-1 agonist

➡one of them is called Exenatide

➡ Very effective; it can produce (2 percent) reduction in the A1C, without any of the side effects associated with insulin or sulfonylurea.

➡It cause real weight loss.

➡MOA:

*It will fix 4 non-functional organ:

1) Suppression glucagon secretion

2) enhance Amylin and insulin secretion.

3)brain satiety

4) Regulation of the GIT empty

➡Side effects:

*weight loss >>>we need that

➡GLP-1 agonist is a protein; so you can't take it orally, it is taken subcutaneous.

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②SGL-2 inhibitors

➡90% of glucose is filtrated by the kidney, then it will be reabsorbed throw SGL (sodium-glucose transport protein), and one of the most important transporters is SGL-2

➡Blocking these transporter result in high glucose exertion, and that what we need in diabetic patients.

➡ The drug names end with **Dapagliflozin** * check the slides and memorize the first one .

➡ Decrease the fasting glucose as well as A1C by (0.7-1) units.

➡Side effects:

1) Weight lost
2) UTI>> very common side effect (10% of the population).
3) Polyuria

- Which is better SGL2 inhibitors or GLP1? GPL1agonist Because they don't produce a common side effect.

#Do we use insulin in type 2 DM?!

Yes; in two cases:

①If the patient come in the third phase, and we use with him glargine as a base-line. We don't use sulfonylurea or megnilitide; because patient in the third phase has very low number of beta cells, so there is no insulin to stimulate the release of it.

*If the patient doesn't response to glargine, then we will treat the patient as type 1 DM

②IF the patient A1C equal 10 or 11 unit, then we should use insulin to have a fast reduction as well as potent reduction (more than 2 units reduction), and these characteristics aren't found in the type 2 DM drugs.

◊Gestational diabetes

➡In the third trimester, the pregnant women appears to have insulin-resistant diabetes

➡The drug of choice is Insulin.

➡Amyral or metformin are prescribed but they are off-label; because we need high control of glucose levels during pregnancy, as it could harm the fetus, since he/she highly susceptible to diseases.

- Please have a look at the slides

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