The Endocrine System

☑ Sheet ☐ Slide ☐ Handout

Number:

Subject: **Clinical introduction to diabetes**

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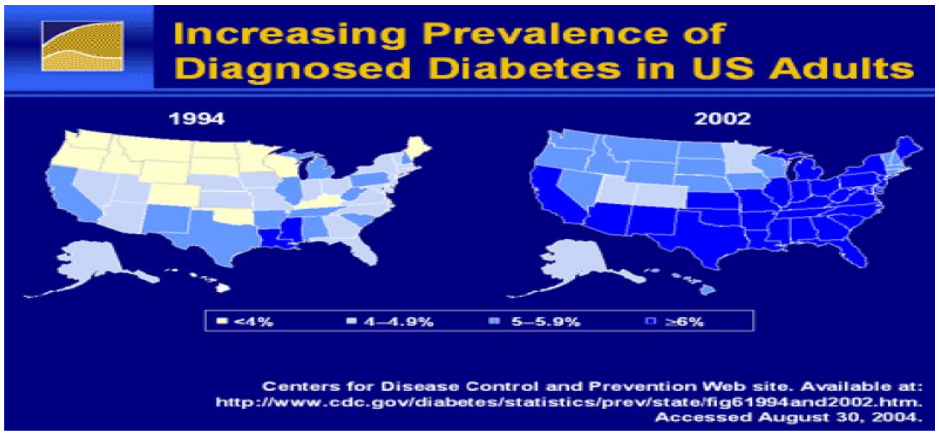
Date:

Price:

- Topics of the lecture:
  - Epidemiology
  - Physiology and pathophysioloigy
  - Role of incretins
  - Types of diabetes
  - Course of the disease
  - Obesity, physical activity and dibates type 2
  - Clinical risk factors
  - Diagnosis
  - Treatment
- Notes:
- The sheet was written in an order that differs from the record.
- Most of the lecture is repetition to what we know about diabetes.

❖ Epidemiology

- Diabetes is a common disease, affecting a lot of people in the population.
- The color shows prevalence, darker color>>> higher prevalence.



- The prevalence in the United States is around 8% in the adult population as well as in Western Europe.
- In Jordan the numbers are higher than 10% or 12% as they are associated with our lifestyle, genetics (genetic makeup in the region), lack of physical activity and obesity/ being over-weight.
- 17% -18% of the Jordanian adults (25 yrs<) are diabetics.
- 8% of the Jordanian adults are pre-diabetics which means that they have impaired glucose tolerance **(IGT).**
- So nearly 25% of the population are either diabetic or pre-diabetic patients.

- NOTE: these numbers are changing and every 10 years new studies are done.
- NOTE: Some people say that one of each 2 Jordanians is diabetic or around 75% of the population is diabetic but these numbers are not accurate. But it's still a common disease in our country.
- 83% of the females are overweight or obese.
- 80% of the males are overweight or obese.
- Type 2 diabetes is known to occur in old people, but with the increased childhood obesity in the last 15-20 years, type 2 diabetes is also occurring in teenagers.
- So these numbers show that the diabetes state in Jordan is bad. But when we compare it with the nearby region, it is relatively better. As in some parts in the Gulf, the prevalence of diabetes reaches 30% and more.
- Some of the Gulf countries are among the highest 10 in diabetes prevalence.

❖ Physiology and pathophysiology:

- **Normally:**
- Glucose regulation is a very complex process and many hormones are involved in its regulation. One of the most important hormones is insulin secreted by pancreas. And we all know that once a person has eaten a meal >>> glucose concentration will be elevated in the blood>>> insulin is secreted to lower it down.
- But it is a **multiple** hormone process:

GLP-1: glucagon like peptide 1

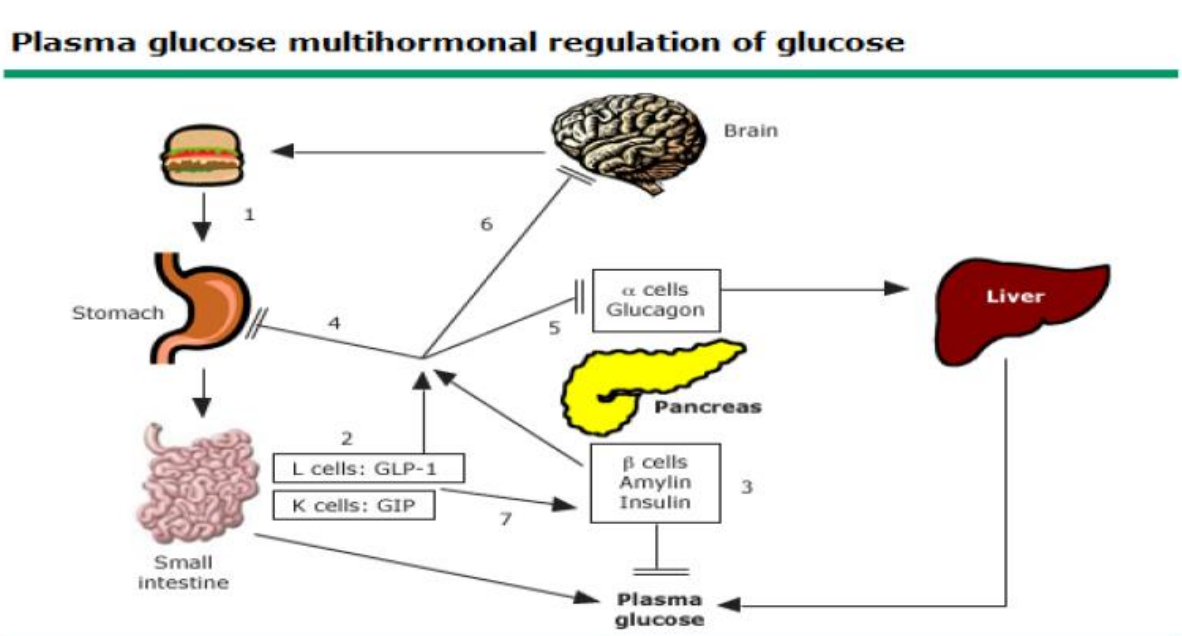
GIP: glucose dependent insulinotropic polypeptide, also known as gastric inhibitory peptide.

1. **Insulin** is co-secreted with **amylin** hormone (peptide hormone) and they work together in this process.
2. **Incretins**: a group of metabolic hormones that stimulate a decrease in blood glucose levels.

- **Insulin** acts on glucose transporters to increase glucose uptake into fat and muscle tissues. But this happens only when glucose levels are elevated in the blood (i.e. after glucose reaches the circulation). So, is there any way by which we can decrease glucose levels even before glucose reaches the circulation (i.e. before being absorbed from the intestines into the blood)?

  Yes. And, this is what incretins do.

- After ingestion of food, the body has to be ready for its next mission, which is to absorb the consituents of food, get them into the blood, and then to secrete insulin, tracking most of the glucose and amino acids to the two largest parts of the body, fat and muscle. To do so, the body makes something to raise insulin even before food constituents are absorbed. These are the **incretins.**
- Incretins are GLP-1 and GIP. They are secreted from the intestine, act on pancreatic beta cells and stimulate insulin secretion.
- Also insulin works with GLP-1 to inhibit glucagon release, which is not required after food ingestion.
- Note: GLP-1 is very important in pharmacology as many drugs work on it.
- Both amylin and incretin inhibit gastric emptying and decease appetite- especially incretins - in a complex mechanism. Why do the do so?
  Incretins stimulate a decrease in glucose levels. They do so by two mechanisms:
  a- By increasing insulin secretion → More glucose is going into tissues.
  b- By decreasing the rate of gastric emptying and suppressing appetite → less glucose is going into the circulation.
  In either way, they decrease glucose levels.
- That is the normal physiology, and diabetes results from problems in this normal mechanism. And remember that there are different types of diabetes resulting from different causes.

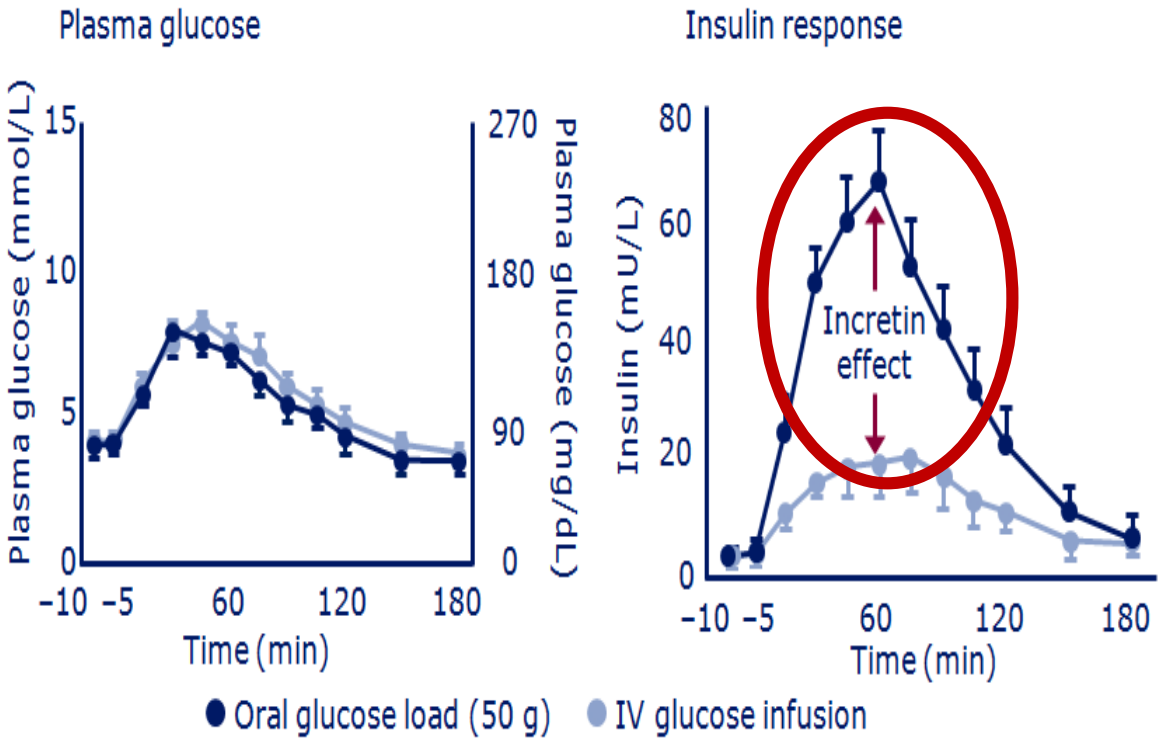


In healthy individuals, (1) ingestion of food results in (2) release of gastrointestinal peptides (GLP-1 and GIP) as well as (3) pancreatic beta cell hormones (insulin and amylin). GLP-1 and amylin, in particular, have inhibitory effects on (4) gastric emptying, (5) glucagon release, and (6) appetite. (7) Following the absorption of food, GLP-1 and GIP promote insulin secretion, otherwise known as the incretin effect. In diabetes, these steps are disrupted.

❖ The role of incretins:

- As mentioned before, they increase insulin secretion, to understand their role well notice the figure below.
  - When glucose is ingested **orally** > >> insulin will increase.
  - Also when glucose given **IV** >>> insulin will increase.
- However the increase in insulin in both cases is **not the same** as the secretion is much better when glucose is ingested orally and it is low when glucose is given IV → the reason behind this difference are the **incretin hormones (mainly GLP-1) that are secreted when glucose is ingested orally**.
- Incretins show an **augmenting effect** on insulin secretion.

- Due to their important role in insulin secretion there are 2 types of anti-diabetic drugs that work on incretins.



❖ Types of diabetes:

1. Type 2 diabetes:

- The common type, 90% of the diabetic cases are type 2.
- And occurs in old patients.
- There is **RELATIVE** insulin deficiency.
- There is a problem in glucagon as it is raised when it should not be.
- Deficiency in incretins.
- Amylin secretion is impaired.
- There is also insulin resistance >>> more likely to be linked to genetics.
- To understand it well :

→The patient has insulin resistance >>> the body tries to compensate by increasing the amount of insulin released by the pancreas >>> over long time this will cause exhaustion to beta cells >>> then beta cell destruction will occur decreasing its ability to do its function>>> so this ends up with insulin deficiency (insulin in not enough) coupled with insulin resistance>>> RELATIVE deficiency. And this resistance increases with increasing age as well as weight.

- Insulin resistance does **NOT** always end up with diabetes but the chance of developing diabetes is higher. And each over-weight person has degree of insulin resistance which increases as the weight increases. For example a person who is obese with a family history of diabetes has a very high chance to develop diabetes during his lifetime.
- Females with PCOS (polycystic ovary syndrome. Commonly known as تكيّس المبيضين) are usually obese, have insulin resistance and they have **brownish discoloration** at the back of the neck, axilla or the groin, known as ***Acanthosis Nigricans***. This brown discoloration is due to **insulin resistance** >> so any patient with this clinical sign is usually type 2 diabetic patient.
- Signs and symptoms develop over long time.
- Type 2 more likely to occur in old people according to textbooks. However, clinically this is not always the case as teenagers are sometimes diagnosed with type 2 diabetes and it is usually after puberty.

Remember that glucagon raises glucose level in the blood antagonizing insulin.

2. Type 1 diabetes:

- There is an **ABSOLUTE** insulin deficiency caused by **destruction** of beta cells.
- Occurs in young patients, usually children, with 2 peaks at ages from 4-6 and 10-14>> before puberty.
- Little bit less than 10% of the cases.
- The underlying cause is **acute or sub-acute autoimmune** destruction of beta cells.

- Unlike type 2 the onset of the disease is relatively **quick**, within one week only, the health status of a normal child will deteriorate badly and insulin will be almost zero.
- The cause behind this sudden autoimmune destruction to beta cells is still not well-known, however there are many theories that suggest **possible causes** (not confirmed) such as:
  - **Viral infection**. (Most probable suggestion).
  - **Vitamin D deficiency**.
  - May be related to **maternal age** >> the older the mother at the time of pregnancy, the higher the likelihood of type 1.
- In this type, some antibodies can be detected such as glutamic acid decarboxylase antibodies in addition to other types of antibodies. And these antibodies are used in diagnosis.
- The treatment is to give the patient **insulin** (insulin is available as a drug in different preparations, mentioned later in the sheet) **OR** give the patient drugs that **increase** insulin secretion from beta cells such as Sulfonylureas.

- *Note: the doctor mentioned that sulfonylureas are used in the treatment of type 1 diabetes. However it is used most of the time for type 2 diabetes.*

❖ Notes:

- **NOTE:** the rest 2% are with other types of diabetes.
- Knowing the type of diabetes is very important as it has many implications on the patient, his life style and treatment. for example:
  - a young patient aged 18 years old with hyperglycemia >> it is very important to know whether he is type 1 or 2 diabetic patient as this will affect his life style and treatment.
  - Obese patient with hyperglycemia >> more likely to be type 2 diabetic.
- As mentioned, both types of diabetes are linked to genetics and that appears in mono-zygomatic twin studies in which the genetic composition is identical:

- When one of the twins is type 1 diabetic patient >> the risk of the second to develop diabetes is 50%
- When one of them is type 2 diabetic patient >> the risk of the second is 90%.

>>> So the genetic relation to diabetes is found in both types but more obvious in type 2.

- REMEMBER: the problem in diabetes in general may be in the insulin itself or its function (resistance). And when we know the problem in each type of diabetes we will know how the drugs work, some are GPL-1 analogs while others are amylin analogs. There are around 7 to 8 different types of drugs that are available nowadays to treat diabetes, mentioned later.

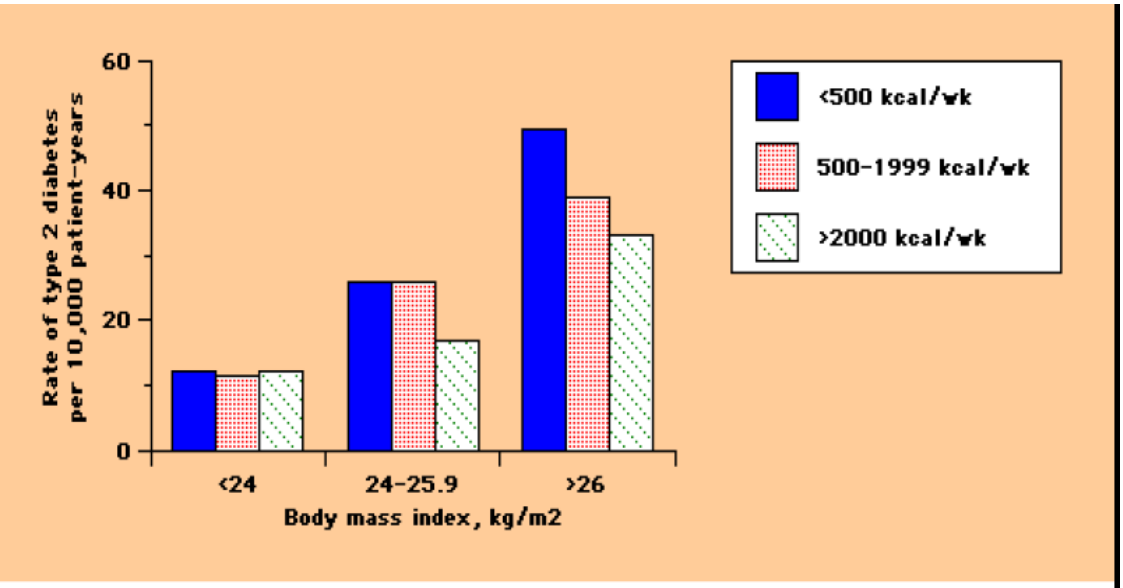
❖ The course of the disease in type 2:

- The patient will come to hospital after long time of the onset of the disease, after 5 or 10 years. However, insulin resistance is found many years before.
- At zero time >> clinical diagnosis
- Insulin resistance >> up to 20 years before diagnosis, which means that the human body can maintain low level of insulin and deal with it for very long time >> and when insulin secretion starts to decrease gradually >> glucose levels, whether fasting or postprandial, will start to increase >>> clinical signs start to appear. So as mentioned, the disease process is long in type 2 unlike type 1.
- So when the diabetes is diagnosed (at zero time in the figure below), 50% of the beta cells have been lost already.
- Diabetic patients have a **fasting blood glucose level** of **126.**

Blue color shows insulin

- **Notes about Slide 7 and 8 :** not very important
  - They are from the American diabetes association.
  - They show the medically described types of diabetes.
  - There are a lot of types but the most important as we know are type 1 and 2. And the remaining types are classified under the name “Others”.

❖ Obesity, physical activity and diabetes type 2:



Importance of body weight and exercise on development of type 2 diabetes Adjusted incidence of type 2 diabetes mellitus in 5990 men in relation to body mass index (BMI, in kg/m2) and the level of physical activity (in kcal/wk). The risk of type 2 diabetes was directly related to BMI, while regular exercise was protective except for men with a BMI below 24. Data from Helmrich, SP, Ragland, DR, Leung, RW, Paffenbarger, PS, N Engl J Med 1991; 325:147.

Regarding the figure:

- White color > high physical activity
- Blue color > low physical activity
- BMI: body mass index(مؤشر كتلة الجسم) which equals =the weight / hight^2, and the normal range between 19 to 25 , 25- 29.9 is overweight ,30 and above is obese

- As seen in the figure as the weight **increases** the incidence of type 2 diabetes **increases** between different groups.
- As the physical activity **increases,** the incidence **decreases** within the same group.
- A lot of studies proved that life style modification, moderate physical activity and weight reduction reduce the risk of diabetes type 2 by 60% which means that diabetes can be prevented.

❖ Clinical risk factors of diabetes :

1. **Family history:** person whose mother or father is diabetic is at higher risk of developing diabetes.
2. **Being over-weight or obese.**
3. **Physical Inactivity.**
4. **Some ethnic origins.**
5. **Prediabetic stage:** whether they have IFG (impaired fasting glucose) or IGT (impaired glucose tolerance).
6. **Gestational diabetes** (GDM): females with GDM are at higher risk of developing type 2 diabetes in the future.
7. **Insulin resistance:** that is associated with many disorders such as PCOS, hypertension and cholesterol problems.

IGT and IFG are terms used to describe pre-diabetic stages.

❖ Signs and symptoms:

1- **Thirst feeling** that result in increased water drinking.

2- Increase in the frequency of urination.

These are the two major signs, then many other signs may appear:

3- Problems in the kidneys

4- Cardiovascular system: the most common causes of death among the diabetics are the myocardial infarction **MI** and strokes.

❖ Diagnosis:

There are many criteria for the diagnosis of diabetes such as:

- **Fasting blood glucose is 126** and above >> this is one of the criteria for the diagnosis

- Oral glucose tolerance test (فحص محلول السكر): is a medical test in which glucose is given and blood samples are taken afterwards to determine how quickly it is cleared from the blood. After two hours of ingesting glucose, the **glucose level is 200 and above.**

Note that in type 1 there is no need to reduce weight. However life style modification is very important.

- **6.5% of the blood glucose is bounded** to hemoglobin.

NOTE: these numbers are important as there isn't other way to diagnose diabetes without using numbers so they should be known.

NOTE: the hidhlighted statement is quoted from wikipedia.

❖ Treatment :

1. **Changing life style** :
   - Reduce weight if over weight.
   - Increase physical activity.
   - Healty diet.

Normally, only 5.7% of glucose is bound to hemoglobin

2. **Drug therapy:**
   - **<u>Type 1 :</u>**

     Simply, Insulin.
   - **<u>Type 2 :</u>**

     A lot of drugs with different mechanisims as there are multipule defects and causes.

   1. **Insulin-depentent drugs :**
      - Insulin replacement >>> by giving the patient insulin (for type 1 mentioned).

- Drugs that increase insulin secretion from beta cells, such as **Sufonylureas**.

2- Drugs that improve the action of the insulin to deal with the resistence such as:

- **Metformin**:
  - ✓ from group known as Biguanides
  - ✓ it is the corner stone in the treatment of diabetes
  - ✓ commonly known as (مساعد السكري)
  - ✓ many actions: mainly it works on the insulin receptor in the liver as it reduces gluconeogenesis, reduces liponeogensis from fatty tissue, slows glucose absorption from GIT.
  - ✓ very effective, cheap.
  - ✓ **first drug of choice** in the treatment of diabetes according to the American and European guidelines.

3- Insulin-independent drugs:

A- soduim glucose cotransporter inhibitors SGLT2:
- They induce the excretion of excess glucose in the urine.
- Relatively new drugs that have been approved for use last year.
- They work on the **kidney**s.
- **Expensive with plenty of side effects.**

B- Some drugs increase the levels of GLP-1 but they are very expensive.

C- Amylin analogs.

D- Dopamine agonists : modestly effective

- NOTE: these drugs will be discussed in details in the next two lectures.

Metformin sometimes is used to reduce weight, however this is NOT labeled use for it. In addition it is usually ineffective and not recommended.

❖ Types of insulin :

- Classified according to **duration of action**:

1. **Ultra- short insulin**: from 3-5 hours, given with meals.
2. **Short acting**: Regular, 6-8 hours.
3. **Intermediate acting**: NPH (Neutral Protamine Hagedorn), 8-12 hours.
4. **Intermediate—long**: Insulin Detimir, 12-14 hours.
5. **Long acting**: Insulin Glargine, for 24 hours and more.

Sorry for any mistake,
Wish you all best of luck~

فكابدوا المجد حتى ملّ أكثرهم ... و عانق المجد كم أوفى و من صبرا