The Endocrine System

PHYSIOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	10
Subject:	Pancreas Physiology
Done By:	Sinamis Drei
Corrected by:	Hashim A. Mohammad
Doctor:	

Date: **20/6/2016**

Price: **10**

بسم الله الرحمـــن الرحيم

This sheet is going to discuss Diabetes , its risk factors , pathogenesis and consequences . MAKE SURE you understand it very well.

NOTE: This sheet was written according to the recording of section 1.

NOTE: Things written in Italic were not mentioned during the lecture. READ THEM to understand.

- In physiology , there are two major types of diabetes (there are more than two types in pathology):

  1. Type I diabetes , also called **insulin-dependent diabetes mellitus (IDDM)** or **Juvenile diabetes mellitus** , is caused by lack of insulin secretion. The usual onset occurs at about 14 years of age. Body mass is either low or normal.

  2. Type II diabetes , also called **Non-insulin-dependent diabetes mellitus (NIDDM)** or **adult-onset diabetes ,** is caused by decreased sensitivity of target tissues to the metabolic effects of insulin , that is often called insulin resistance. The usual onset occurs after the age of 30, often between ages of 50 and 60 years. In the recent year, however , there has been an increased incidence of diabetes among younger individuals. Here, patients are usually obese.

  - **Other differences between the two types are shown in the figure below :**

TABLE 78-2
Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 years	Usually >40 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

*Insulin-dependent diabetes (IDDM). Juvenile diabetes.

*Non-insulin-dependent diabetes (NIDDM). Maturity-onset diabetes.

- First , let's start with major symptoms that appear on diabetic patients:
  1. increased thirst.
  2. excessive urination.
  3. weight loss (in diabetes mellitus type I).

  Note : this sheet is going to discuss the reasons behind such symptoms.

- **In the previous lecture, we discussed the major effects of insulin deficiency on carbohydrates metabolism , these are:**
  1. No glucose transport and uptake to adipose tissue and skeletal muscles.
  2. More glucose output than input in the liver.
  3. Decreased glucose reabsorption in the renal tubules → glycosuria.
  4. Brain is not affected.

  However, the most important effect of insulin deficiency is that the enzyme "**Hormone-sensitive lipase**" in adipocytes becomes strongly activated .

  - When insulin levels are normal , the enzyme is usually suppressed and it becomes strongly activated in case of insulin deficiency. We don't need very high amounts of insulin to keep the enzyme suppressed (very little amount of insulin is enough to suppress the activity of this enzyme).

  - When insulin is deficient, the Hormone- sensitive lipase is activated. Consequently, triglyceride hydrolysis is stimulated by the action of the enzyme. Thus, free fatty acids and glycerol are released into the blood, some of these fatty acids are utilized for energy and others will be used as substrates to produce keto acids, which, in turn, leads to metabolic acidosis.

  - **These keto acids are:** Beta-hydroxybutyric acid and acetoacetic acid.

  - ***Mechanism :*** *In case of insulin deficiency , cell utilization of glucose becomes increasingly lower ,and utilization of fats (through stimulation of Hormone-sensitive lipase) and proteins increases for the sake of energy. The shift from carbohydrates to fat metabolism increases the release of keto acids into the*

plasma more rapidly than they can be taken up and oxidized by tissue cells. As a result, the patient develops severe metabolic acidosis which in association with excessive formation of urine (mentioned later in this sheet) lead to severe acidosis that results in diabetic coma and death unless the condition is treated immediately with large amounts of insulin. (Guyton and Hall)

- Previously, it was said that excessive urine excretion (polyuria) drags electrolytes with it, which leads to electrolyte depletion. These electrolytes include sodium, when sodium is excreted it becomes replaced with hydrogen ions, which is another contributor to acidosis.

- Thus, the release of ketone bodies as well as sodium excretion lead to acidosis.

- **What about proteins ?**

  In case of insulin deficiency, protein synthesis becomes increasingly lower (no energy for protein synthesis as glucose uptake and utilization by cells is inhibited) , while protein break down to amino acids increases .

  - Amino acids that result from protein breakdown are either used for production of energy for the cell OR they are used as substrates for glucose synthesis in gluconeogenesis (which is actually a problem as it leads to additional increase in plasma glucose concentration).

  - Failure to use glucose for energy leads to increased utilization and decreased storage of fat and proteins. Therefore, a person with severe untreated diabetes mellitus (type I) suffers **rapid weight loss** and ***asthenia*** (lack of energy) despite eating large amounts of food (polyphagia) . Refer to Guyton and Hall

---

- Insulin deficiency and decreased glucose uptake lead to the following:
  1. hyperglycemia (high blood glucose levels) .
  2. Glycosuria .
  3. Osmotic diuresis → That is , high osmotic pressure in the urine due to the high concentration of glucose . ***As a result , the tubular reabsorption of fluid is greatly decreased, and the overall effect is massive loss of fluid in the urine causing dehydration of the extracellular fluid which in turn causes compensatory dehydration of the intracellular fluid . Thus, polyuria , intracellular and extracellular dehydration and increased thirst are all major symptoms of diabetes mellitus type I .***

  - Loss of massive amount of fluid in urine leads to electrolyte depletion , loss of nitrogen that is found in the amino acid that result from protein catabolism in the urine , and loss of ketone bodies metabolized from free fatty acids in the urine (ketonuria) .

  - " you should be able to distinguish between ketogenesis , ketonuria , and ketonemia " – said Dr . Saleem ☺

  - Coma in diabetes might be a result of multiple actions :
    1.Severe acidosis can end up with diabetic coma and death if not controlled .

    2. The hyperosmolarity of the plasma (due to elevated blood glucose levels) causes unconsciousness and hyperosmolar coma .

    3. Accumulation of lactic acid causes coma.

    4. Brain edema occurs in about 1% of children with diabetes and it can cause coma
    5. Coma is sometimes caused by hypoglycemia (this is not related to diabetes)

  - Normal blood glucose concentration: about 90mg/100dl. If you are to measure your plasma glucose level during fasting, it will be always

90mg/100dl (constant) → *being constant is what makes your blood glucose level normal even if it was 70mg/100dl.*

- When plasma glucose level is below 40mg/100dl→ Coma (hypoglycemic coma).

- Patients with Diabetes mellitus type I who always get injections of insulin often keep some sweets in their pockets so as to avoid hypoglycemic coma that could result when the insulin injected to the subject is higher than the need of the body to transport glucose into cells resulting in hypoglycemia

  Note1: insulin injection should be appropriate with the plasma glucose concentration. Therefore, the dose of insulin following a meal of rice should be higher than that injected after a meal of vegetables, for example. An injection of insulin that exceeds the dose needed would result in hypoglycemic coma.

  Note2: Recently, a device called ***insulin pump*** *is being used to inject an adequate amount of insulin after measuring the specific blood glucose level so that the patient would avoid Hyper- and Hypo-glycemia.*

❖ Treatment of diabetes :

- Type I diabetes: effective treatment of DM type I requires administration of enough insulin so that the patient would have carbohydrate, fat and protein metabolism that is as normal as possible.

- Type II diabetes: dieting and exercise are usually recommended in an attempt to induce weight loss and to reverse insulin resistance (through up-regulation of insulin receptors). If this fails, drugs may be administrated to increase insulin sensitivity, stimulate increased insulin production by the pancreas or decrease the absorption of glucose .(refer to Guyton and Hall)

- **Multiple classes of drugs and agents used can be classified according to the mechanism of action:**

  1. Insulin sensitizers with primary action on the liver → they facilitate the action of insulin on the liver (by increasing insulin sensitivity).

  2. **Insulin sensitizers with primary action on peripheral tissues** → they facilitate the action of insulin on peripheral tissues.

  3**. Insulin secretagogues** → they increase secretion of insulin by the pancreas .

  4. **Agents that slow down the uptake of carbohydrates**.

- **If none of these drugs worked out, then exogenous insulin must be used to regulate blood glucose**.

❖ Diabetes – If not treated – leads to :
1. Renal failure → due to osmotic diuresis and polyuria.
2. Coronary heart failure
3. Increased risk for cancer

❖ Cardiovascular diseases are the most prominent. In fact, more than 65% of people with diabetes die from heart diseases. Adults with diabetes have heart diseases death rates 2-4times higher than normal adults. Also, strokes account for 20% of diabetes-related death (2-4 times higher than normal individuals).

❖ Obesity

- **Fat cell size Vs. Fat cell number :**
  In adults, obesity results from an increase in fat cell SIZE, while Fat cells number remains constant (the number is determined in childhood).

- Three major ways to determine whether an individual is obese or not:
  1.**The relationship between Height and Weight**

  - ✓ For males → Height – 100 = weight

Example : Height = 170 cm , weight = 70kg .

  - ✓ For females → Height – 105 = weight
    Example : Height=170 cm , weight = 65 kg .

2. **Measuring the waste** → waste size should be less than half of your height.

3. Body mass index

$$\text{Body Mass Index} = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in m)}}$$

BMI = 25.82

- < 18 → underweight
- < 18.5 → thin for height
- 18.6 - 24.9 → healthy weight
- 25 - 29.9 → overweight
- > 30 → obesity

❖ **Glucagon :**

- Has a relationship with insulin, similar to that between PTH and Calcitonin.
- Glucagon, like insulin, is a protein.
- Glucagon is the second major pancreatic hormone that is secreted from Islets Of Langerhans, that is responsible for short – term regulation of plasma glucose level (minute by minute).
- Glucagon's principle target tissue is the Liver.
- Like insulin, glucagon is first released into the portal circulation and is then transferred to the liver, where it participates in the regulation of hepatic metabolism.

- **Important note:** Amino acids released after digestion of protein meals appear to be the major glucagon secretagogues (NOT glucose)

- **Glucagon acts on the liver and is involved in the carbohydrates and lipids metabolism.**

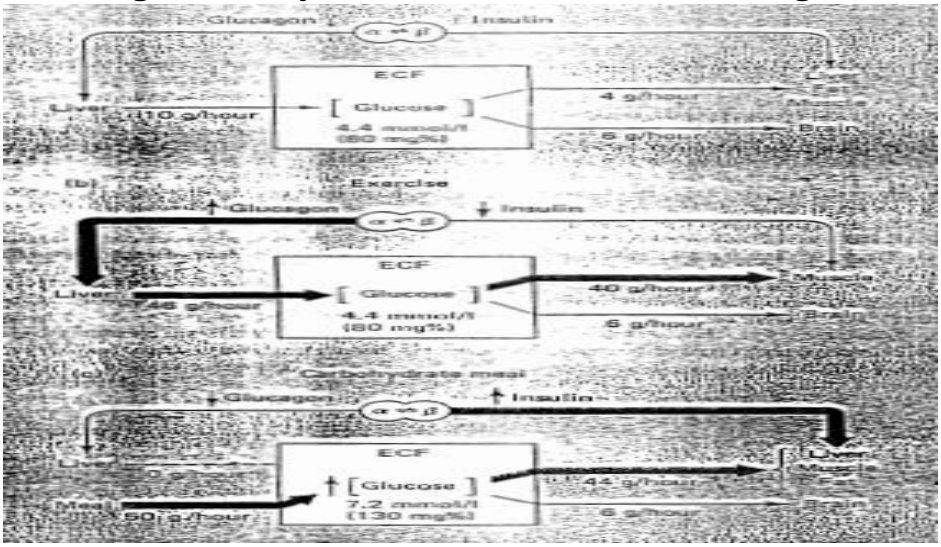
- **Glucagon stimulates the following :**

  - **Glycogenlysis**
  - **Gluconeogenesis**
  - **Ketogenesis**

- Glucagon doesn't only act on the liver, rather, it has a glycogenlytic effects on the cardiac and skeletal muscles, and a lipolytic effect on adipose tissue. Glucagon also promotes the protein breakdown in several tissues, this protein breakdown effect, however, appears to be more important when tissues are exposed to pharmacological concentrations of glucagon, and liver is the main target tissue when glucagon is present in physiological levels**.**

- **These points about glucagon are really important.**

❖ **The levels of glucose , glucagon and insulin during rest , exercise and following a carbohydrate meal are shown in the figure below :**



Who you were, who you are, and who you will be are three different people.

Note: This page is a complement for sheet 8

Effect of Vitamin D on Bone and Its Relation to Parathyroid Hormone Activity

- Vitamin D plays important roles in both, bone absorption (resorption), and bone deposition.
- The administration of **extreme quantities** of vitamin D causes **absorption of bone**. In the absence of vitamin D, the effect of PTH in causing bone absorption is greatly reduced or even prevented.
- Vitamin D **in smaller quantities** promotes **bone calcification**. One of the ways in which it does this is to increase calcium and phosphate absorption from the intestines. However, even in the absence of such increase, it enhances the mineralization of bone through another mechanism of effect that is still not well known.

Guyton and Hall textbook
(Page 962 in the 12th edition)