endocrine system

physiology

Sheet Slide

number	8
Done by	Zahra Muneer
Correction	Mohammed AbuHani
Doctor	Saleem

In this sheet, I referred to the record, the book, and last year sheet.

Things written in Italic were not mentioned during the lecture.

Good Luck ☺

Insulin functions on almost all the tissues of the body to facilitate the entry of glucose.

Important and vital tissues for survival like the brain, kidney tubules, intestinal mucosa, and red blood cells use glucose spontaneously without depending on insulin. If such tissues depended on insulin, diabetic patients will not survive, as any problem in insulin will cause insufficient oxygen to the body leading to death (red blood cells), low blood volume (kidney), and problems in absorption (intestine).

Table 19–3. Effect of insulin on glucose uptake in tissues in which it has been investigated.

Tissues in which insulin facilitates glucose uptake
Skeletal muscle
Cardiac muscle
Smooth muscle
Adipose tissue
Leukocytes
Crystalline lens of the eye
Pituitary
Fibroblasts
Mammary gland
Aorta
A cells of pancreatic islets
Tissues in which insulin does not facilitate glucose uptake
Brain (except probably part of hypothalamus)
Kidney tubules
Intestinal mucosa
Red blood cells

What's insulin? Insulin: regulates the amount of glucose in the blood.

Insulin helps control blood glucose levels by signaling the liver, muscle and fat cells to take in glucose from the blood. Insulin, therefore, helps cells to take in glucose to be used for energy. If the body has sufficient energy, insulin signals the liver to take up glucose and store it as glycogen.

In a normal person, the blood glucose concentration is narrowly controlled and is usually between 80 and 90 mg/100 ml of blood in the fasting person each morning before breakfast. *This concentration*

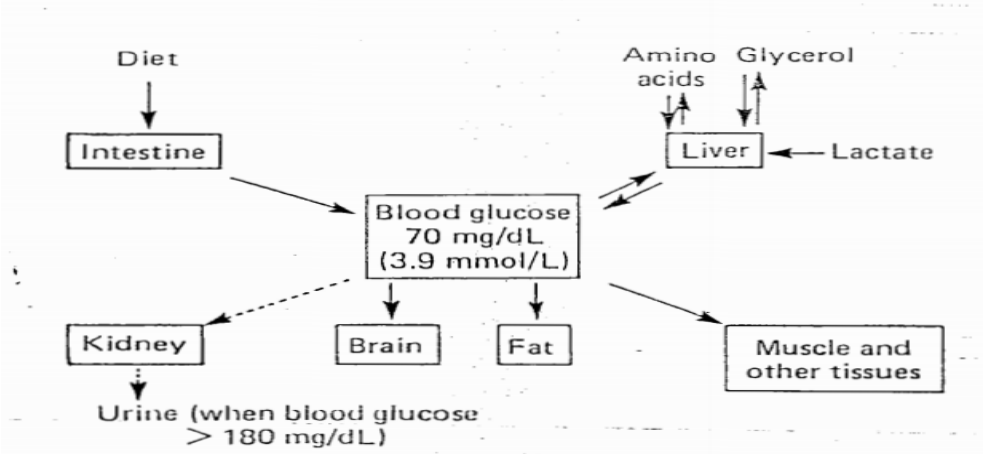


Figure 17–14. Blood glucose homeostasis, illustrating the glucostatic function of the liver.

increases to 120 to 140 mg/100dl during the first hour or so after a meal, but the feedback system for control of blood glucose rapidly return glucose concentration back to the control level, usually within 2 hours after the last absorption of carbohydrates. (no glucose appear in the urine when glucose levels are normal)

When the concentration of glucose in the blood is 180 mg/dl or below and no glucose is in the urine, the brain usually is not affected as it does not need insulin and the supply of glucose is constant.

30-40% of glucose goes into fat, 5% to the liver, and the remaining is metabolized in muscles and other tissues.

In a fasting liver, glycogen is broken down and the liver adds glucose to the blood. With prolonged fasting glycogenolysis is decreased and gluconeogenesis is increased and protein catabolism and also free fatty acids are released to blood (normally).

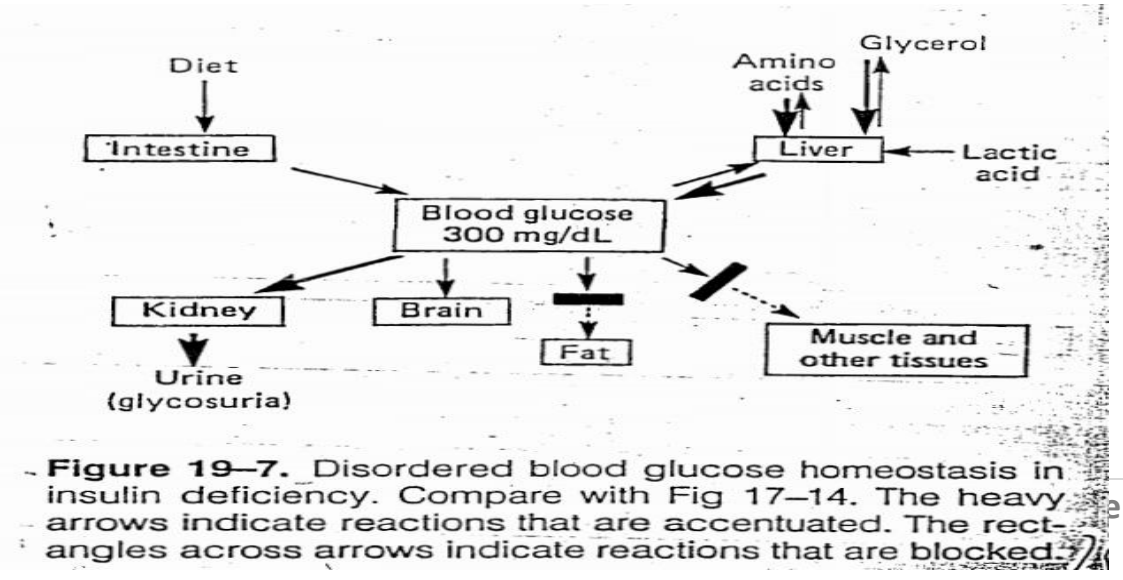


Figure 19–7. Disordered blood glucose homeostasis in insulin deficiency. Compare with Fig 17–14. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reactions that are blocked.

During hyperglycemia, glucose appears in urine because the concentration of glucose becomes very high (above 180) →so there is glycosuria -the brain usually is not affected; however, in severe diabetic patients when glucose levels reach above 500 or below 40mg, the brain is affected. In hyperglycemia, glucose conversion to fat is affected, and muscles and other tissues are affected as well. The amount of glucose coming out of liver is more than that going into of liver. → [disordered blood glucose homeostasis]

Hyperglycemia→ abnormality in the metabolism of carbohydrates and abnormality in fat and protein metabolism.

The major effects of insulin deficiency:

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.

Insulin deficiency→ Diabetes

Type 1 Diabetes	*Type 2 Diabetes*
Also called insulin-dependent diabetes mellitus (IDDM) or Juvenile diabetes mellitus; usually genetic	Also called Non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes
*is caused by lack of insulin secretion. The usual onset occurs at about 14 years of age. Body mass is either low or normal. **Destruction of beta cells due to viral infections or autoimmune disorders.*	*is caused by decreased sensitivity of target tissues to the metabolic effects of insulin, and that is often called insulin resistance. The usual onset occurs after the age of 30, often between ages of 50 and 60 years. In recent years, however, there has been an increased incidence of diabetes among younger individuals. In type 2 diabetes, patients are usually obese.

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.

Symptoms:

1. Increased thirst and hunger

2. Excessive urination.

3. Weight loss (in diabetes mellitus type I).

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: diet 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.
  - 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 beta cells in 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: mainly because of hypertension and high levels of circulating cholesterol and other lipids. In diabetic patients, atherosclerosis and severe coronary heart disease develop.

3. Increased risk for cancer (diabetes decreases immunity).

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

Abnormality of Lipids in Insulin Deficiency:

There are enzymes which are usually suppressed when insulin level is normal, because they need very slight amount of insulin to be suppressed, but these enzymes become strongly activated in the case of insulin deficiency. Consequently, triglyceride hydrolysis is stimulated by the action of these enzymes. Thus, free fatty acids and glycerol are released into the blood, and consequently, the plasma concentration of free fatty acids begins to increase within minutes. These free fatty acids then become the main energy substrate used by essentially all tissue of the body except the brain. In this condition, the body totally depends on the energy coming from free fatty acids (to enhance the state of the body in the absence of insulin).

<u>The excess usage of fats during insulin deficiency causes ketosis and acidosis.</u> Insulin deficiency causes excessive amounts of acetoacetic acid

to be formed in the liver cells and depresses utilization of acetoacetic acid in peripheral tissue. Some of the acetoacetic acid is converted into Beta-hydroxybutyric acid and acetone. These two substrates, along with acetoacetic acid, are called ketone bodies (acidosis) and their presence in large quantities in the body fluids is called ketosis. In this condition, there's urination which causes dehydration, and excessive urine excretion (polyuria) drags electrolytes with it, which leads to electrolyte depletion. These electrolytes include sodium. When sodium is excreted, it is replaced with hydrogen ions, which are another contributor to acidosis.

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

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

Abnormality of Proteins in Insulin Deficiency: causes protein depletion and increases plasma amino acids.

Protein synthesis becomes increasingly lower (*no energy for protein synthesis as glucose uptake and utilization by cells is inhibited*), while protein break down (catabolism) to amino acids increases. Amino acid levels in the plasma rise considerably, and most of the excess amino acids are used either directly for energy or as substrates for glucose synthesis in gluconeogenesis (which is actually a problem as it leads to additional increase in plasma glucose concentration→ hyperglycemia). *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).*

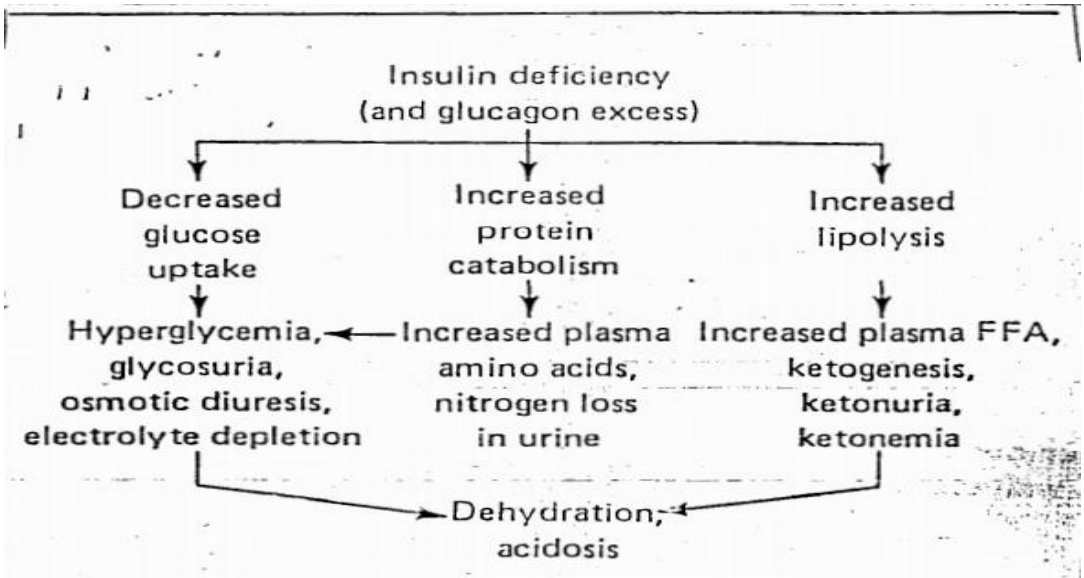


Figure 19–10. Effects of insulin deficiency. (Courtesy of RJ Havel.)

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.

4. Increased protein catabolism to amino acids→ nitrogen loss in urine

5. Increased lipolysis of free fatty acids→ketogensis, ketonuria, and ketonaemia

Coma in diabetes might be a result of multiple actions:

1. Severe acidosis can lead to 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 may cause coma.

4. Brain edema occurs in about 1% of children with ketoacidosis and it can cause coma.

5. Coma is sometimes caused by hypoglycemia [when glucose level is 40 mg or below (this is not related to diabetes)].

Obesity

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:

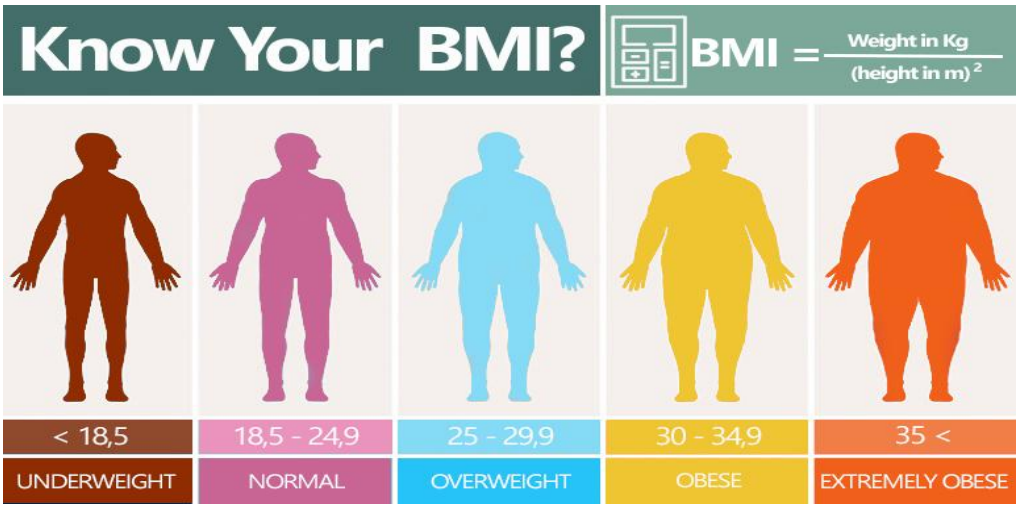
1. The relationship between Height and Weight→

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 waist → waist size should be less than half of your height.

3. Body mass index



Glucagon: the most potent hyperglycemic hormone and functions on carbohydrate metabolism, but the main stimulus for glucagon secretion is the increase in amino acids which is very strange. Glucagon is the major pancreatic hormone in regulation of body fluid metabolism (glucose, amino acids, and free fatty acids also are involved in regulation of body fluid metabolism).

**glucagon is secreted in response to hypoglycemia or low blood concentrations of glucose, but elevated blood levels of amino acids as would be seen after consumption of a protein -rich meal appear to be the major stimulus to secretion of glucagon.

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 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 the liver is the main target tissue when glucagon is present in physiological levels.

Have an idea about glucose supply and level of glucagon and insulin during rest, exercise, and during taking a meal:

Rest	Exercise	Meal
Rest: 10g/hour glucose from liver 4g/h into muscles, liver, fat 6g/h into brain	Exercise: glucagon increase . 46g/h from liver 40g /h to muscle 6/h to brain	Carb nothing from liver 50g/h from meal 44g/h into liver 6g/h into brain

Brain is not affected usually.

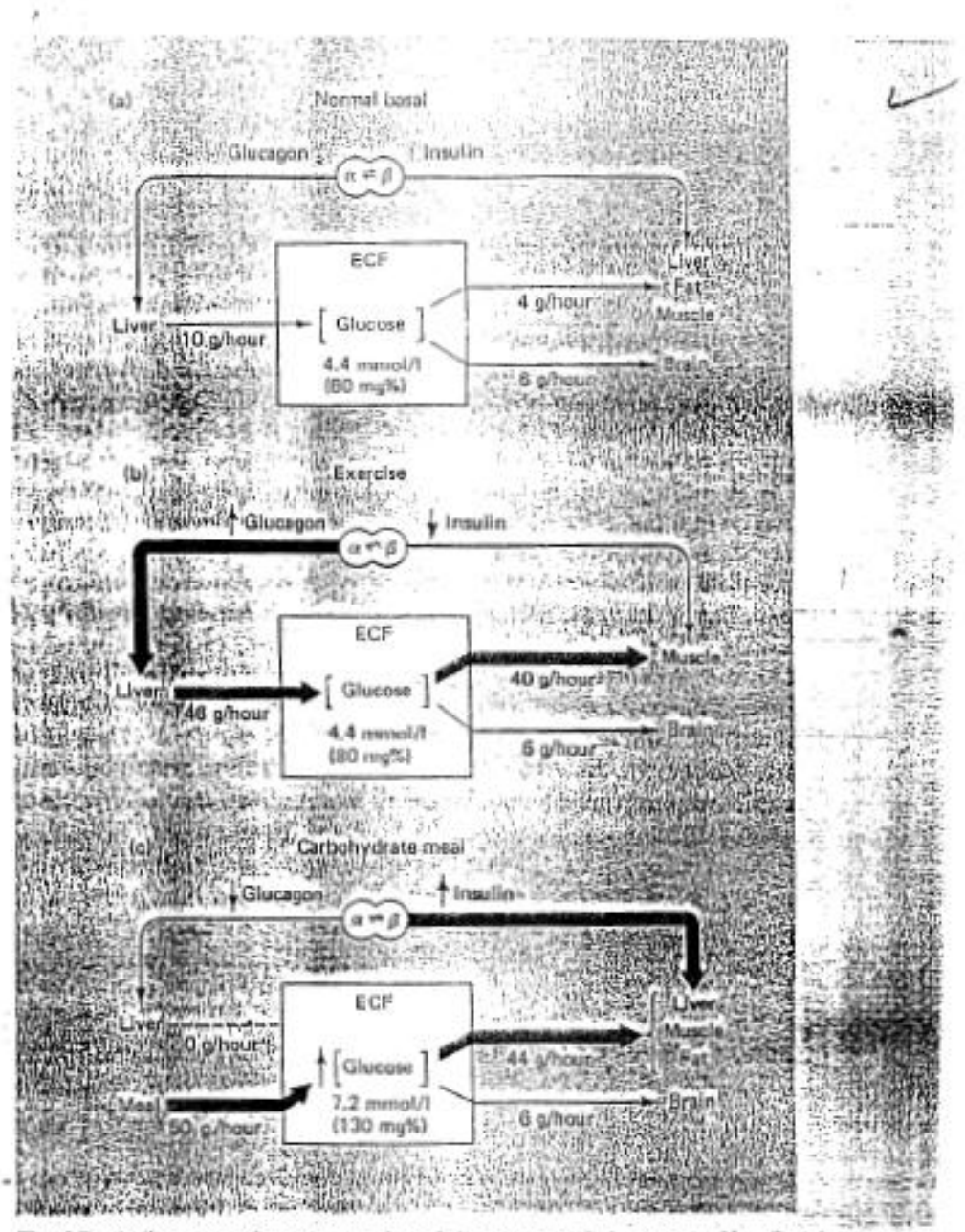


Fig. 4.7 A diagrammatic representation of the patterns of glucagon and insulin release at rest (**A**), during exercise (**B**) and following a meal of carbohydrate (**C**) and the consequential changes in glucagon distribution. (From Unger, R. H. (1976) Diabetes **25**, 136.)