

Министерство здравоохранения республики Беларусь
Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
Обсуждено на заседании кафедры
Протокол №7 от 30.08.2017

МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: **Нарушения углеводного и липидного обменов**

Theme: **Disorders of carbohydrate and lipid metabolisms**

Время 3 ак. часа

1.Actuality of the theme. Disorders of carbohydrate metabolism are extensive and are the leading link in pathogenesis of many diseases. The most frequent and severe form of carbohydrate metabolism pathology is diabetes mellitus. Diabetes mellitus is a disease resulting from absolute or relative insulin deficiency and accompanying by disturbance of metabolism mainly, carbohydrate one.

The disturbance of lipid metabolism leads to change in their functions and development of pathological processes, such as: obesity, malnutrition, dyslipoproteinemia, lipodystrophy and lipodosis.

Learning goals of the lesson: to study etiology and pathogenesis of diabetes. To consider neurogenic, endocrine and metabolic mechanisms of obesity. To study risk factors, etiology and pathogenesis of atherosclerosis.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know typical forms and causes of violations of carbohydrate metabolism.
2. To be able to explain causes and mechanisms of emergence of hyper- and hypoglycemic conditions.
3. To know modern ideas about etiology and pathogenesis of diabetes, explain a relationship of main functional disorders and metabolic disorders in diabetes.
4. To know main forms of lipid metabolism disorders.
5. To be able to characterize the type of dyslipoproteinemia (DLP).
6. To be able to explain causes, mechanisms and consequences of obesity.
7. To know modern concepts of atherogenesis.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Significance of carbohydrates for the organism (normal physiology disciplines).
2. Scheme of normal glycogen metabolism in the liver and skeletal muscles. Intermediate metabolism of carbohydrates and lipids (biochemistry discipline).

Control questions of the lesson:

1. Typical forms of violations of carbohydrate metabolism. Hypo- and hyperglycemia.
2. Diabetes mellitus (DM): definition, classification, mechanisms of violations of all types of metabolism in diabetes.
3. DM type 1: etiology, pathogenesis.
4. DM type 2: etiology, pathogenesis. Characteristics of main risk factors.
5. Acute and chronic complications of diabetes.
6. Typical forms of pathology of lipid metabolism: classification, etiology, pathogenesis, principles of prevention and correction.
7. Disturbance of cholesterol metabolism: mechanisms of hypo- and hypercholesterolemia.
8. Atherosclerosis: definition, pathogenetic mechanisms and adverse effects.

Calculation of study time

Total study time 3 ac.hours

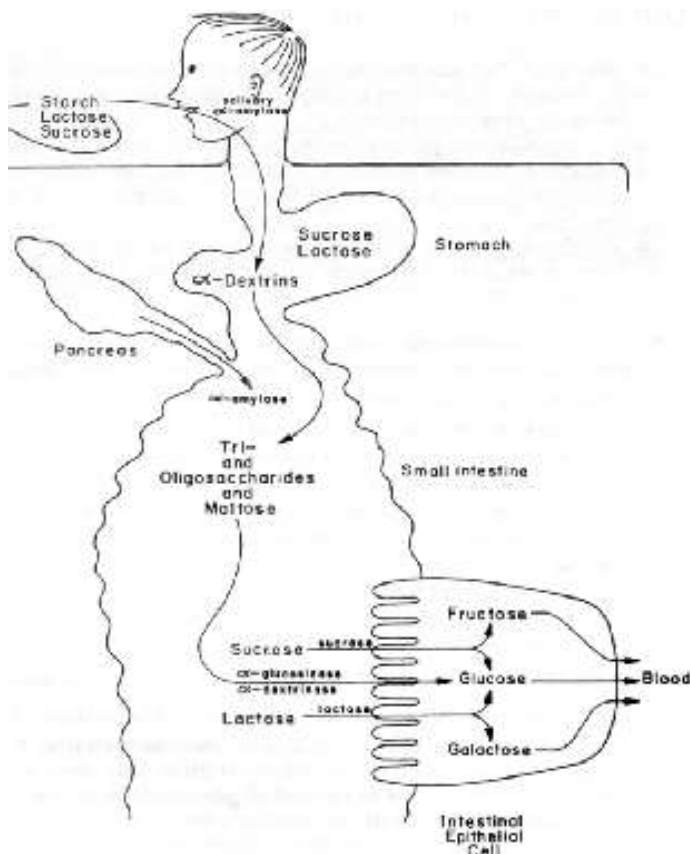
№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Carbohydrates were found out by K.E. Schmidt in 1884. It is a large group of compounds, including sugars and starch, that contain carbon, hydrogen, and oxygen and have the general formula $C_x(H_2O)_y$.

Impairments of carbohydrate metabolism

- impairments of digestion and absorption
- impairments of synthesis, depot and split of glycogen
- impairments of interstitial metabolism
- impairments of excretion of glucose from kidney
- impairments of carbohydrate metabolism regulation



Impairments of digestion

- not sufficiently active digestive enzymes, enzyme systems of phosphorylation and dephosphorylation of carbohydrate

Carbohydrates are transported in enterocytes by two ways:

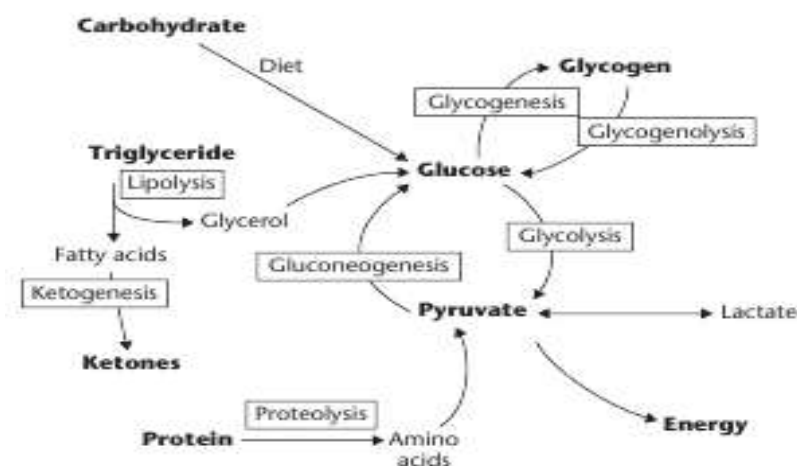
- gradient of concentration by facilitated diffusion with transporters: GLUT 2, GLUT 5
- against the gradient of concentration by the secondary active transport with an expenditure of ATP

Figure 1 digestion and absorption of carbohydrate

Impairments of absorption

- intestinal enzymopathies
- Violation of production/release of pancreatic juice (pancreatic acinar tissue lesion)
- Action of enzymatic poisons, blocking the phosphorylation and dephosphorylation
- Lack of Na
- disorders of circulatory in the intestine

Impairments of synthesis, storage and split of glycogen



Decrease in glycogen synthesis and its storage

- ↓ tone of parasympathetic NS
- hypoxia
- loss of hepatocytes
- hypo-, avitaminosis B, C
- violation of endocrine regulation (DM, hyperthyroidism, Addison's disease)

- hereditary diseases

Figure 2 Pathway of glucose metabolism in cell

Increase in split of glycogen and decrease in its storage

- stimulation of sympathetic NS

- ↑ production of hormones that stimulate glycogenolysis (epinephrine, glucagon, thyroxine, growth hormone)
 - intense muscular work
 - fever, shock, emotional stress
- insufficiency of glycogen substrate → FA and proteins are used for energy processes in the cell → excessive formation of KB → hyperketonemia, ketonuria

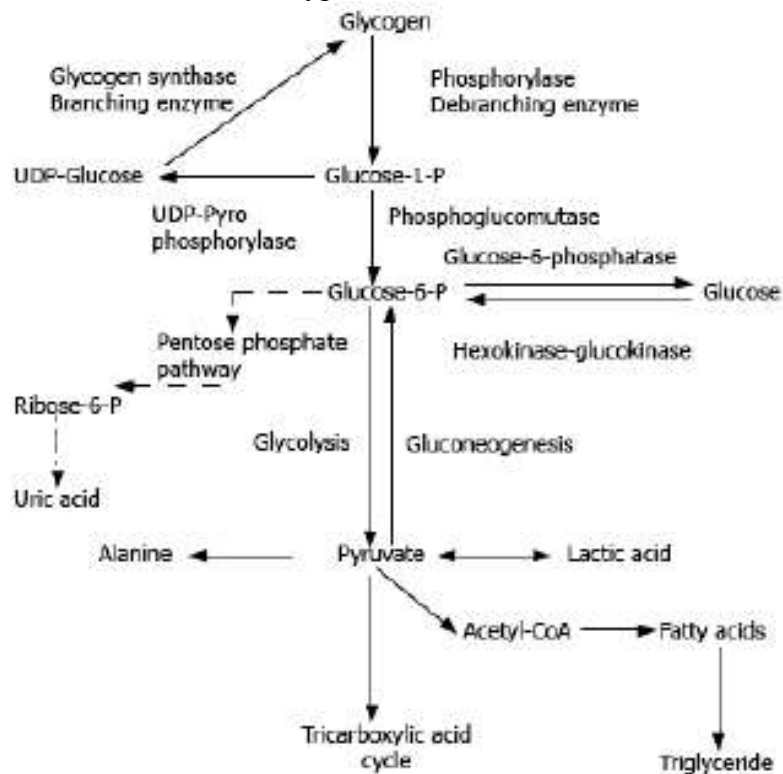


Figure 3 Simplified pathway of glycogen synthesis and degradation

Glycogenosis (glycogen storage disease)

It is a diseases caused by genetic defects in enzymes for glycogen splitting, that lead to excessive glycogen accumulation in different organs (liver and skeletal muscle).

There are: 2 forms: liver and muscular

14 types of glycogenosis (type0 – typeXIII)

Liver

Disturbed is in hepatocytes. Common symptom is hypoglycemia in postabsorbtion period. There are:

Type I (Gierke's disease)

Type III (disease Corey and Forbes)

Type IV (Andersens' disease)

Type VI (Hers' disease)

Type IX (Haga disease)

Musclar

Impaired glycogenolysis providing energy to skeletal muscles. Occur during exercise → pain, muscle cramps, weakness, fatigue. Hypoglycemia is not typical. There are:

Type V (Mc-Ardl disease)

Type VIII (Tarui disease)

Interstitial metabolism

- anaerobic Gl splitting (glycolisis)
- aerobic Gl splitting (oxidative decarboxylation of pyruvate to acetyl CoA, citric acid cycle, pentosophosphate shunt)
- gluconeogenesis

- interconversion of hexose
- formation of pentose, needed for nucleotide synthesis
- synthesis of fatty acids (from acetyl CoA and glycerin)

Impairments of interstitial metabolism

(Interstitial metabolism is carried out at the cellular level involves all the conversion of carbohydrate from the cell entering to the formation of final product → CO₂ and H₂O)

Causes:

1. Hypoxia (switches the cellular metabolism from aerobic to anaerobic oxidation → split of glucose → excess lactate → lactic acidosis)
2. Liver function disorders (violation of gluconeogenesis in hepatocytes → lactic acid → blood → lactic acidosis (in norm part of the lactic acid is resynthesized into glucose and glycogen)
3. Hypovitaminosis B1 (deficit of cocarboxylase → ↓ synthesis of acetyl-CoA → accumulation of pyruvic acid → partial metabolism in lactic acid → lactic acidosis → when ↑ of pyruvic acid by 2-3 times → sensitivity disorders, neuritis, paralysis (↓ synthesis of acetylcholine => failure of nerve pulses transmission)
4. Hereditary defects of enzymes: defect of gluconeogenesis enzyme: lack of Gl-6-P in glycogen storage disease I type (Gierke's disease) → expressed lactic acidosis)
5. Iatrogenic factors

Impairments of excretion of glucose from kidney

- serum glucose > 8,8-9,9 mmol / l → excrete from the urine
- when filtration is decreased → glucose not detected in the urine even when glucose is significantly higher than the renal threshold
- tubulopathy → impaired reabsorption → glucose can be present in urine even in norm or decreasing level of glucose → "renal diabetes"

Impairments of carbohydrate metabolism regulation

- Neural
- Hormonal
- Renal
- Substrate

Neural

Sympathetic impulses → release of adrenaline → stimulation of glycogenolysis → hyperglycemia
Parasympathetic impulses → ↑ excretion of insulin → ↑ Gl flow into the cell → hypoglycemia

Hormonal regulation of metabolism

Hormone	Action on carbohydrate metabolism	Action on protein metabolism	Action on fat metabolism
insulin	hypoglycaemia ↑ glucose uptake by cells ↓ hepatic glucose output	↑ protein synthesis ↑ amino acid uptake by cells	↓ plasma FFAs Inhibits hormone-sensitive lipase Stimulates fat synthesis
glucagon	hyperglycaemia ↑ hepatic glucose output stimulates gluconeogenesis	—	↑ plasma FFAs ↑ lipolysis
epinephrine	hyperglycaemia ↑ hepatic glucose output ↓ insulin secretion ↑ glucagon secretion		↑ plasma FFAs ↑ lipolysis
GH	hyperglycaemia ↓ glucose uptake by muscle and adipose tissue	↑ protein synthesis ↑ amino acid uptake	↑ plasma FFAs ↑ lipolysis
Cortisol	hyperglycaemia	stimulates deamination of	↑ plasma FFAs

		amino acids	↑ lipolysis
T₃	↑ use of all energy substrates inc. glucose	↑ protein degradation	↑ lipolysis
ketones	↓ glucose utilisation by brain (also muscle, kidney, mammary gland etc.)	↓ protein degradation ↓ gluconeogenesis	↓ lipolysis

Insulin — is a polypeptide hormone, MM — 6000 D, consists of the two polypeptide circuits, associated with two disulfide bonds. It is formed in beta-cells as proinsulin on endoplasmic reticulum ribosomes. From a lamellar complex insulin, C-peptide, proinsulin under influence of ions Ca act in vesicles where insulin is deposited associated with a crystal condition cycle. Then there is a vesicle promotion to membrane and insulin release in precapillary space. Insulin is in blood in free and tissue associated condition. Inactivation of insulin, proinsulin and C-peptide occurs in liver (80%) under the influence of glutathion-reductase and glutathion-transferase (insulin degradation can be carried out in kidneys and fat tissue).

The biological effect of insulin is shown on its ability to associate with the specific cytoplasmic membrane receptors (the biggest number of receptors — 250 000 on a cell — hepatocyte, the smallest number — up to 5 000 — fat tissue). 10–15% of receptors are on the membrane. Insulin level is regulated by concentration of insulin in blood. Insulin chemically reacts with a cell receptor, generates a biological signal, which changes process of transport. owing to what a complex insulin-receptor gets into a cell owing to these changes, and then it is splitted by lysosomes.

Insulin independent tissues — CNS, brain cortex, adrenal glands, spermaries, eyes — absorb glucose from blood without participation of the conveyors, started insulin.

The most powerful regulator of insulin secretion is glucose. There are two various points of view on insulin secretion:

1. *Receptor theory* — glucose binds with the specific receptors on the beta-cell membranes, as a result of this chemical interaction there is production of insulin.

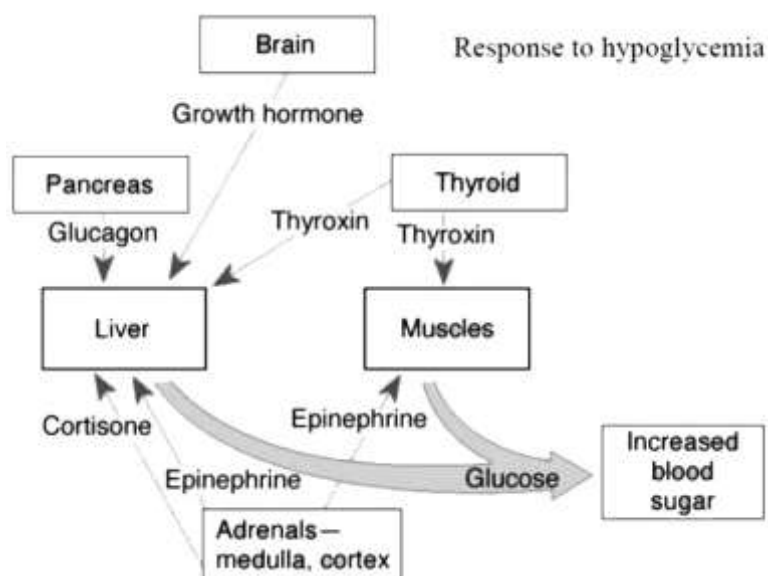
2. *The metabolic theory* — according to this theory glucose gets inside beta-cells and amplifies glycolysis. It promotes an increase of NADP and NADPH, cAMP, there is Ca²⁺ ion accumulation activating cytoskeleton microfilaments which promote insulin release.

Renal Regulation by:

- **filtration** (when filtration is decreased → glucose not detected in the urine even when glucose is significantly higher than the renal threshold). Renal threshold: glycosuria appears ↑ serum Gl > 8,8-9,9 mmol / l
- **reabsorption**. tubulopathy → impaired reabsorption → glucose can be present in urine even in norm or decreasing level of glucose → "renal diabetes

Substrate

border concentration of Gl 5,5-5,8 mmol / l (production in liver = consumption by peripheral tissues), higher level → synthesis of glycogen in the liver and muscles



Hypoglycemia

It is a syndrome testifying about a decrease in blood glucose level (lower than 3,3 mmol/l)

Hypoglycemia testifies about the blood glucose level control impairments

Mechanisms of hypoglycemia

- a decrease in blood glucose inflow
- an increase in glucose utilization by tissues and blood outflow
- combination of mechanism 1 and 2

Types of hypoglycemia

- alimentary
- insulin
- contra-insulin hormone insufficiency
- glycogenic
- hepatic
- diabetes insipidus
- enzymopathia
- autoimmune
- essential
- hypoglycemia in patients with diabetes mellitus

Symptoms of hypoglycemia results from central and peripheral NS impairments:

- in abrupt decrease in blood glucose level caused by hyperadrenalinemia, an increase in sympathetic system activity
- cerebral symptoms prevail in more slow decrease in glucose level

Hyperglycemia

Hyperglycemia is defined as an increase of capillary blood glucose level above N ($>6,1$ mmol/l).

Types of hyperglycemia

- physiologic (compensatory)
- pathologic (impairments of active hormonal homeostasis)
 1. alimentary
 2. neurogenic
 3. convulsive
 4. endocrine
 5. insulin

Diabetes mellitus

Diabetes mellitus is clinically and genetically heterogeneous disease, which is characterized by chronic multihormonal frustration of all metabolism types (metabolic disease N 1) and gradual defeat of all organs and systems.

Etiologic classification of diabetes mellitus

- I. Type 1 (beta-cell destruction usually resulting in absolute insulin deficiency).
 1. autoimmune diabetes — WHO (immune mediated)
 2. essential diabetes
- II. Type 2 (it results from the primary insulin resistency with relative insulin deficiency up to predominantly secretory defect with insulin resistency or without it — WHO).
- III. Other specific types of diabetes.
 1. genetic defects of beta-cell function
 2. genetic defects in insulin action
 3. disease of exocrine pancreas
 4. endocrinopathias
 5. diabetes induced by medicines or chemicals
 6. infections
 7. unusual forms the immune mediated diabetes
 8. unusual forms of immune-mediated diabetes
 9. gestation diabetes

Diabetes mellitus type 1

It is characterized by impairments of carbohydrate metabolism, which are caused by beta-cell destruction, and ketoacidosis aptitude. It is characterized by absolute insulin deficiency and absolute or

relative excess of contra-insulin hormones.

Autoimmune diabetes mellitus is characterized by beta-cell destruction resulting from autoimmune or immune process.

Essential diabetes mellitus is characterized by beta-cell destruction and a decrease in beta-cell number. Etiology and pathogenesis are unknown.

Key link in pathogenesis: progressive Beta-cell destruction of pancreas islets.

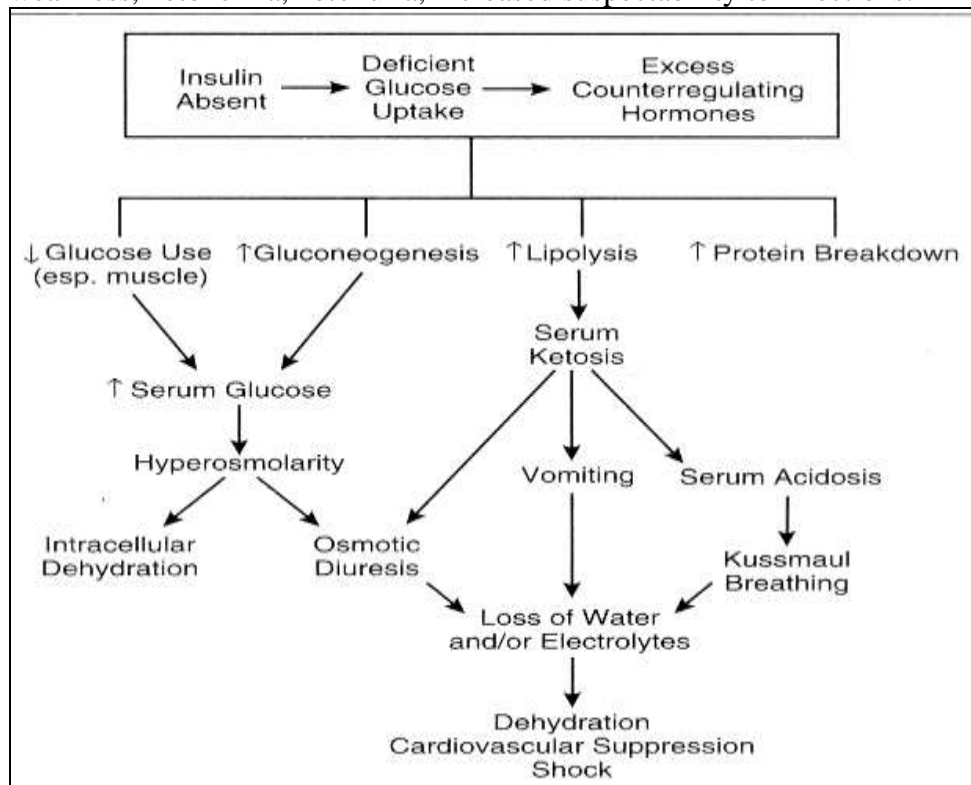
Diabetes mellitus type I is HLA-associated.

Auto-antibodies spectrum in diabetes mellitus type I:

- antibodies to pancreatic islets, to insulin, to glutamate decarboxylase, cytoplasmic antibodies and others
- organospecific — antibodies to thyroglobulin, peroxidase of thyroid gland, gastric parietal cells, hemopoietin, adrenal gland cortex cells, antilymphotoxic antibodies, IgG and IgA.
- non-organospecific — anti-nuclear, mitochondrial, antibodies to smooth muscle fibers, fibroblasts.

Clinical manifestations

polyuria, polydipsia, polyphagia, ketoacidosis, hyperglycemia, glucosuria, weight loss, muscle weakness, ketonemia, ketonuria, increased susceptibility to infections.



Insulin resistance

Classification of insulin resistance

I. According to etiology:

1. abnormalities of beta-cell secretory product: abnormality of insulin molecule, block in proinsulin transformation into insulin
2. clinical antagonists of insulin: an increase of contra-insulin antagonists (growth hormone, cortisol, catecholamines and others), non-hormonal insulin antagonists, defect of insulin receptor, post-receptor defects

II. According to pathogenesis

- primary (before insulin therapy)
- secondary (reaction on insulin therapy)

III. According to defect localization

- pre-receptor
- receptor
- post-receptor
- combined (most often)

Causes of IR:

1. autoimmune reactions

- development of anti-insulin antibodies
 - development of anti-insulin receptor antibodies
- #### 2. defects in the insulin receptor at the cell surface

- defect in receptor processing
- ↓ number of receptors

3. postreceptor defect

4. defective signal transduction (from the receptor to the plasma of cell)

5. ↑ concentration of anti-insulinic hormones

6. abnormalities of beta-cell secretory product:

- abnormality of insulin molecule,
- block in proinsulin transformation into insulin

Diabetes mellitus type 2

Carbohydrate metabolism impairments associated with insulinresistancy and defect in insulin secretion or primary impairments of insulin secretion and moderate insulinresistancy.

So, there are two factors of diabetes mellitus type 2 pathogenesis:

1. insulin resistancy
2. defect in insulin secretion

It is characterized by relative insulin secretion. Age of onset >50 years. It is not directly HLA-associated. It is not characterized by hereditary predisposition. 90 to 100% concordance in twins (type 1 50% concordance in twins).

Clinical course is stable, ketoacidosis is not characteristic (insulin inhibits lipolysis and creates conditions for acetyl Co-A utilization in lipogenesis and steroid genesis).

Type 2 clinical features: insulinresistancy, obesity, hyperlipidemia type IV and V, hypertension, hyperuricemia, nephropathia, accelerated atherosclerosis.

Table 13. Comparative characteristic of diabetes mellitus type 1 and 2

	Type 1	Type 2
clinical	onset>20 years normal weight decreased blood insulin anti-islet cell antibodies ketoacidosis is common	onset>50 years obese normal or increased blood insulin no anti-islet antibodies ketoacidosis rare
genetics	50% concordance in twins HLA-D linked	90% to 100% concordance in twins no HLA association
pathogenesis	autoimmunity, immunopathologic mechanisms, severe insulin deficiency	insulin resistance, relative insulin deficiency
islets cells	insulin early, marked atrophy and fibrosis, beta-cell depletion	no insulinitis, focal atrophy and amyloid deposits, mild beta-cell depletion

Specific types of diabetes

1. Genetic defects of beta-cell function.

Diabetes results from the specific gene defects are referred to this group. Diabetes occurrence is associated with monogenic defect of beta-cell function.

- MODY 1,2,3,4 — maturity onset diabetes of the young — it is diabetes of adults in youth
- mitochondrial gene mutation (mutation of DNA 3243).

For the first time the point mutation of mtDNA was opened in MELAS-syndrome (mitochondrial myopathy, lactate-acidosis, encephalopathy, stroke like syndromes, diabetes associating with sensory loss or without loss of hearing).

- the other forms of diabetes mellitus type 2, which are caused by mutant or abnormal insulin (Chicago, Angelino insulin, impairment of proinsulin conversion into insulin resulting in intermediate

forms of insulin. Intermediate forms of insulin possess only 5–10% of intact insulin biologic activity).

2. Genetic defects of insulin action.

- resistancy to insulin type A
- lipoatrophic diabetes, etc.

3. **Diseases of exocrine part** (pancreatitis, trauma, neoplasia, fibrocalculous pancreas pathology, pancreatectomy, hemochromatosis, etc.)

4. **Endocrinopathias** (acromegaly, Cushing's syndrome, pheochromocytoma, glucagonoma, hyperthyroiditis, somatostatinoma).

5. Diabetes mellitus induced by medicines or chemical substances

- glucocorticosteroids, thyroid hormones, α - and β -adrenergic agonists, a nicotinic acid;
- vacor-remedy for struggle against rodents;
- nitrozamines, nitrozurea;
- pentomidin-remedy for pneumocystic carinii infection treatment;
- cyanides.

6. Viral infections.

Viral infections influence diabetes mellitus occurrence. Viral infections associate with beta-cell destruction: Coxsack B4, cytomegalovirus, congenital rubella, epidemic parotitis

7. **The unusual forms of insulin-mediated diabetes:** physical inactivity syndrome — CNS autoimmune disease (antibodies to glutamate decarboxylase, systemic lupus erythematosus (antibodies to insulin receptor), pigment papillary dystrophy of skin, acanthosis nigricans — pigment papillary dystrophy of skin (antibodies to insulin receptor).

8. **The other genetic syndromes:** Down's syndrome, Turner's syndrome, Klinefelter's syndrome, Laurence-Moon-Bardet-Biedl – insulin defect, a decrease or beta-cell absence)

9. Gestational diabetes

Gestational diabetes

It is defined as diabetes that occurs in a previously non-diabetic pregnant woman. Although this type of diabetes often resolves after delivery, approximately 50% of affected women will not revert to the non-diabetic state after the pregnancy is over. Even in those who do, the risk of developing type II diabetes after about 5 years is higher than normal.

Causes:

The increased energy demands during pregnancy and the continually high levels of estrogen and growth hormone are believed to be the causes of gestational diabetes. Growth hormone and estrogen stimulate insulin release and may result in an oversecretion of insulin, leading to decreased cellular responsiveness. Growth hormone also has some anti-insulin effects, for example, the stimulation of glycogenolysis, the breakdown of glycogen, and the breakdown of adipose tissue. Adiponectin, a plasma protein derived from adipose tissue, plays a role in regulating insulin concentration and resistance; reduced levels of this substance also may contribute to the impaired glucose metabolism and hyperglycemia seen in gestational diabetes. Women who develop gestational diabetes may have subclinical problems with glucose control even before diabetes develops.

Consequences:

Gestational diabetes can negatively affect the pregnancy by increasing the risk of congenital malformations, stillbirths, and large-for-date babies, which can result in problems during delivery. Gestational diabetes is routinely tested for during prenatal medical examinations. Good obstetrical outcomes are dependent on good maternal glycemic control as well as pre-pregnancy weight. Women who have gestational diabetes usually are treated with diet, insulin, or both, as necessary. The use of oral anti-hyperglycemic agents such as sulfonylurea (glyburide) instead of insulin for pregnant women unable to achieve glycemic control with diet alone has been investigated. Findings suggest glyburide may be as effective as insulin in reducing obstetric complications, without increasing the risk of congenital malformations, although further studies are required to ensure the safety of this or other agents

Disorders of metabolism in diabetes mellitus

Absolute or relative insulin deficiency results in energy starvation of muscular and fat tissue. It is characterized by an increase in contra-insulin hormone secretion. All these result in carbohydrate, lipid

and protein metabolism impairments:

1) *Carbohydrate metabolism*

- in muscles, liver – a decrease in glycogenesis
- a decrease in glucose income in fat tissue
- glycogenolysis in muscles and liver, which is influenced by glucagon and adrenaline
- hyperglycemia
- lactacidemia

2) *Protein metabolism*

- prevalence of catabolic processes (particularly in muscles)
- an increase in amino acid and urea blood level
- loss of nitrogen

3) *Lipid metabolism*

- a decrease in fat depot
- an increase in fat level in liver
- an increase in contra-insulin hormone level
- an increase in very-low-density-lipoprotein production in liver

4) *Water-electrolyte metabolism*

- loss of potassium and sodium
- polyuria, dehydration

Clinical manifestations

obesity, polydipsia, polyuria, weakness, weight loss, hyperglycemia, dehydration, hyperosmolar non-ketonic coma.

Complications

- **Acute:** diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic syndrome (HHS), hypoglycemic coma (inadequate dose of insulin), lactacidemic coma
- **Chronic:**
 - ✓ circulatory abnormalities:
 - atherosclerosis;
 - cardiomyopathy (with no apparent coronary arteries pathology);
 - ✓ vascular:
 - macrovascular
 - microvascular
 - ✓ retinopathy;
 - ✓ diabetic nephropathy;
 - ✓ diabetic neuropathy (peripheral polyneuropathy, radiculopathy, autonomic neuropathy);
 - ✓ diabetic foot ulcers.

Diabetic ketoacidosis (DKA)

Pathogenesis:

severe insulin insufficiency → triggers a complex metabolic reactions :

- ↓ glucose utilisation → hyperglycemia and glycosuria
- ↑ GNG → hyperglycemia
- ↓ lipogenesis and ↑ lipolysis → ↑ oxidation of FFA → production of ketone bodies (aceto-acetate, hydroxy-butyrate, and acetone) → hyperketonemia → metabolic acidosis → **coma**

Hyperosmolar hyperglycemic syndrome (HHS)

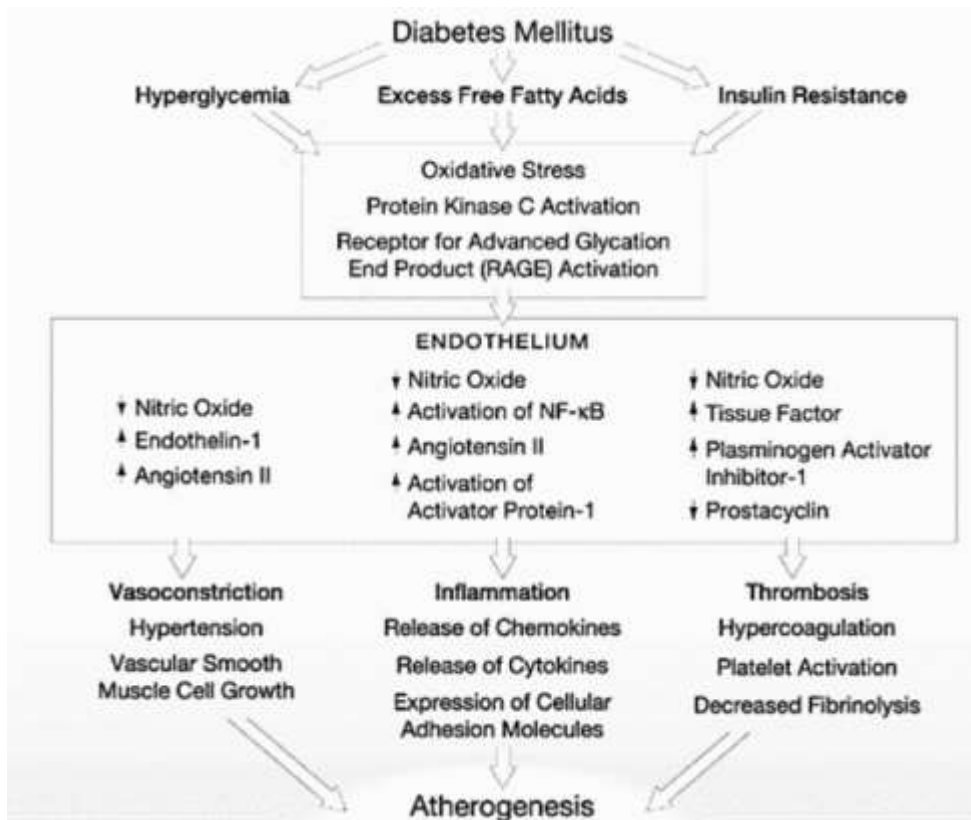
Pathogenesis:

↓↓ insulin (but present) →

1. → it inhibits fat breakdown → lack of ketosis

2. → its effectivity is less than needed for effective glucose transport → **severe hyperglycemia** (**>600 mg/dL**) → glycosuria and polyuria → body fluids depletion → intracellular dehydration → **severe hyperosmolarity** (**>320 mOsm/L**) → neurologic disturbances (stupor, **coma**)
severe acidosis and ketosis are generally absent in the HHS !!!

Hypoglycemic coma (inadequate dose of insulin)



Diabetic retinopathy

Pathomechanisms:

- increased retinal capillary permeability, vein dilation
- formation of microaneurism and hemorrhages
- narrowing of small arteries lumen
- neovascularisation and fibrous tissue formation within the retina
- retinal scars formation → blindness

Diabetic Nephropathy

- rise in glomerular filtration rate
- glomerular lesions
- increased glomerular permeability
- microalbuminuria (30 to 300 mg/day)
- diffuse glomerulosclerosis
- massive proteinuria - nephrotic syndrome
- systemic hypertension
- progression to CRF

Diabetic Neuropathy

Pathogenesis:

- vascular damage of vasa nervorum
- metabolic damage of nerve cells
- non-enzymatic glycation of proteins

First morphologic and functional changes:

- axonal degeneration preferentially involved unmyelinated fibers (in spinal cord, the posterior root ganglia, peripheral nerves)

DISTURBANCES OF LIPID METABOLISM

Impairments of lipid metabolism

- impairments of digestion and absorption
- impairments of transport of lipids and transition them into the tissues
- impairments of intermediate metabolism and deposit in adipose tissue
- impairments oxidization of lipids is in tissues

Impairments of digestion and absorption:

- 1) deficit of pancreatic lipase which is reason of violation of breaking up of fat in the lumen of thin bowel (gut) to fat acids, monoglycerides, glycerin;
- 2) deficit of bilious acids which are reason of violation of fat emulsification and decline of activity of pancreatic lipase;
- 3) increased peristalsis of thin bowel and damage of its epithelium which displays by violation of activating of pancreatic lipase;
- 4) surplus in the meal of ions of Ca and Ig, when appear insoluble in water salts of fat acids;
- 5) avitaminosis A and B, insufficiency of choline, violation of process of phosphorylation, that is accompanied decreasing of suction of fat.

Impairments of transport:

Fractions of lipids determine in blood: a) general lipids (triglycerides – 0,4 – 1,8 mmol/l); b) free fatty acids (to 180 mg/l); c) cholesterol (5,2- 6,1 mmol/l), d) ketone bodies.

The basic transport form of lipids in an organism is lipoproteins, which show by itself the complexes of lipids and albumens in different correlations. These correlations show up physically as a density which is multiplied at growth of particle of albumen. Distinguish such types of lipoproteins:

- chylomicrons (CM) contain a 2% proteins and 98% lipids (by basic appearance of triglycerides), in a norm in plasma out of adopting a meal they are not contained;
- very low density lipoproteins (VLDL) contain a 10% proteins and 90% lipids (mainly triglycerides).
- low density lipoproteins (LDL) 25% proteins and 75% lipids (mainly free cholesterol and its ethers), capable to transport a cholesterol in cells, contain, that is why is most atherogenic.
- high density lipoproteins (HDL) a 50% proteins and 50% lipids (phospholipids and triglycerides), capable to «take» away surplus of cholesterol from the surface of endothelium and muscle and to carry them in a liver, then it goes back into blood or excretion with a bile.

Multiplying the amount of general lipids in the blood (over 2 mmol/l) is named hyperlipemia which can be: 1) alimentary, 2) transport and 3) retention.

Alimentary – begins show up through 2-3 hour after consumption in fatty meal, achieving a maximum through 4-6 hour, through 9 hour the level of fat in blood goes back to a norm. It is the physiology phenomenon.

Transport – is observed during activating of lipolysis, increased mobilization of fat from a depot and it transport to liver. Reasons – increasing the amount some hormones: a) growth hormone, b) thyrotropin, [thyroid stimulating hormone, thyrotrophic hormone], c) thyroid hormones, d) adrenalin, e) glucagons

Retention – arises up at the delay of transition of neutral fats from blood to tissues and linked time-lagged breaking up of chylomicrons on the luminal surface of endotheliocytes from the decline of activity of lipoprotein lipase (LPL). Condition that is possible:

- 1) surplus entering organism or delays of excretion from the organism of salt (NaCl) which is inhibitor of LPL;
- 2) decline of product heparine by tissue basophiles, which at normal terms stimulates production and activate LPL;
- 3) violation of correlation between the concentration of insulin and counter-insulin hormones. Insulin activates LPL, and its antagonists repress it, that is why there is expressed hyperlipemia at diabetes mellitus;
- 4) entering of bilious acids into the blood (at icterus), which repress LPL;
- 5) damage of luminal surface of endothelium cells, that is accompanied the decline of activity of LPL.

Hyperlipoproteinemia is multiplying maintenance in plasma of blood of lipoproteins (one or a few classes) At Fridreksen (1967) distinguish 5 types of HLPE, which can take purchased or inherited character:

According to classification of WHO hyperlipoproteinemias are following:

Types	Hereditary origin	Acquired	Manifestations
Type I ↑ChM	Deficiency lipoproteinlipase	SLE	high plasma cholesterol, CM and TG, extracellular deposit of TG in a skin as xanthoma, hepatosplenomegaly as result of fat deposit of in stroma of liver and spleen; abdominal colics from microembolism of mesenteries vessels; propensity to acute pancreatitis. Atherosclerosis does not develop.
Type IIa - ↑LDL	Familial hypercholesterinemia (deficiency receptors to LDL)	Hypothyroidism	Level of general cholesterol in blood in 2-4 times are higher as normal. plural xanthomas; development of atherosclerosis; coronal insufficiency, (development of heart attack of myocardium, even for children).
Type IIb - ↑LDL+↑VLDL	Combine familial hypercholisterinemia	Nephritic syndrome	
Type III - ↑remnant particles of ChM+↑IDL	Familial dys-β-lipoproteinemia Familial hyperlipoproteinemia the III ^d type	Obesity	high level of cholesterol and TG is in plasma; xanthomas in skin of lines of palms and in places of pressure of rings; atherosclerosis of coronal arteries, peripheral vessels and vessels of brain; obesity, diabetes mellitus, hypothyroidism.
Type IV - ↑VLDL	hyperpre-β-lipoproteinemia (familial essential hyperlipemia) Combine familial hyperlipidemia	Diabetes mellitus	common obesity; liver fatty dystrophy; diabetes mellitus, chronic disease of kydnes, angiopathies of organs, fatty deposits in a retina
Type V - ↑ChM + ↑VLDL	Familial hypertriglycerides	Alcohol intoxication	increase concentration of chylomicrons, tryglicerids and cholesterol; acute pancreatitis; xanthomas; neuropathy; paresthesia of hands and feet.

Legend: ↑ - increase Ch – chylomicrons, LDL – low density lipoproteides, VLDL – very low density lipoproteides, IDL – intermediate density lipoproteins.

Atherosclerosis

It is defined as a chronic focal inflammation of the arterial wall characterized by the formation of cholesterol-rich fibrofatty plaques in the intima, intimal thickening and smooth muscle proliferation leading eventually to ischemia of an organ due to blockage of the arterial lumen.

Risk Factors:

- Modifiable
 - ✓ Dislipidemia (hypercholesterolaemia, hypertriglyceridaemia, increased LDL concentration)
 - ✓ Obesity
 - ✓ Smoking
 - ✓ Hypodynamia
 - ✓ Alcoholism
 - ✓ Hypertension
 - ✓ Stress
- Nonmodifiable
 - ✓ age
 - ✓ Male sex

- ✓ Having close relatives who have had some complication of atherosclerosis (e.g. coronary heart disease or stroke)
- ✓ Genetic abnormalities, e.g. familial hypercholesterolemia

Theory of atherosclerosis

- Infiltrative
- Hemodynamic
- Coagulopathic
- Monoclonal
- The response to injury

Infiltrative: the role of hypercholesterolaemia, primary in the pathogenesis of AS is entering of lipids from blood to the vessel wall.

Hemodynamic: role of hypertension:

hemodynamic instability in hypertension → endothelial damage → proliferation of SMC → LP entering in to the vessel wall.

Coagulopathic: the role of Tr

Tr fixing to the endothelium (as a result of violation of blood viscosity) → triggers a cascade of processes that stimulate the proliferation of SMC → ultimately leads to the formation of AS-plaque

Monoclonal: the role of the proliferation SMC: SMC proliferation in the intima presented with monoclonal myocytes (all cells from single cells predecessor)

The response to injury:

Damage of the endothelium → Impaired function and loss of endothelial cells → Fixing of Tr to the damaged endothelium → Proliferation of SMC → Capture by macrophages and SMC of modified LP → Formation of foam cells → Death of foam cells with release of their contents → Change of SMC phenotype from contractile cells type to the synthesising cells type → production of collagen → connective cover of AS plaque

Types of modified LP

- Peroxide-modified
- Glycosylated LDL, HDL
- Auto-immune complexes LP-Ab

Current Concept:

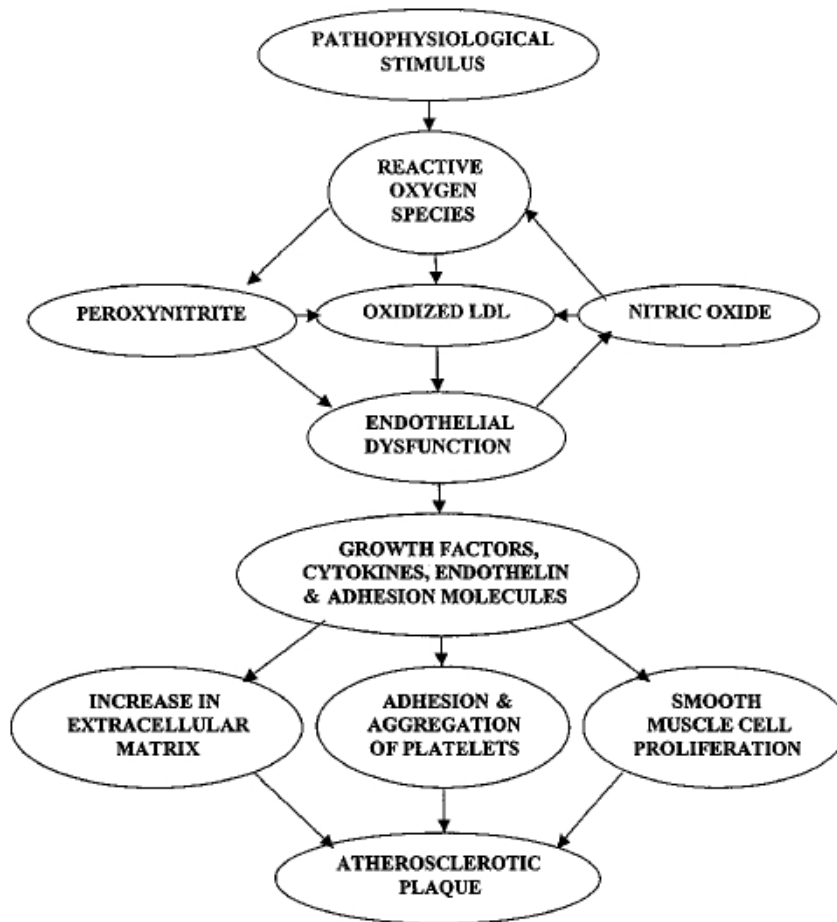
It views the primary event as injury to (or dysfunction of) arterial endothelium, which may be produced by hypercholesterolemia, mechanical injury, hypertension, immune mechanisms, toxins, or viruses or their infectious agents. Hyper-lipidemia may initiate endothelial injury, promote foam cell formation, act as a chemotactic factor for monocytes, inhibit macrophages motility, or injure smooth muscle cells.

Development of atheromatous plaque:

1. monocytes and lipids enter into subendothelium, sometimes with platelet adhesion and aggregation at the injury site;
2. platelets (and perhaps also monocytes) release mitogenic (i.e. mitosis or growth including) factors (e.g., platelet-derived growth factor and possibly fibroblast growth factor-a);
3. these growth factor cause migration and proliferation of smooth muscle cells into intima, with the production of connective tissue matrix proteins (collagen, elastin, glycosaminoglycans, and proteoglycans);

4. monocytes and smooth muscle cells engulf lipids and transform into lipid-laden cells, this process is mediated by the beta-VLDL receptors, and the scavenger receptors, which recognize modified LDL-cholesterol;

5. the aggregation of foam cells covered by fibrous cap is the atheromatous plaque.



Vessels involved:

- lower bdominal aorta
- coronary arteries
- popliteal arteries
- descending thoracic aorta
- internal carotid aorta
- circle of Willis

Complications of

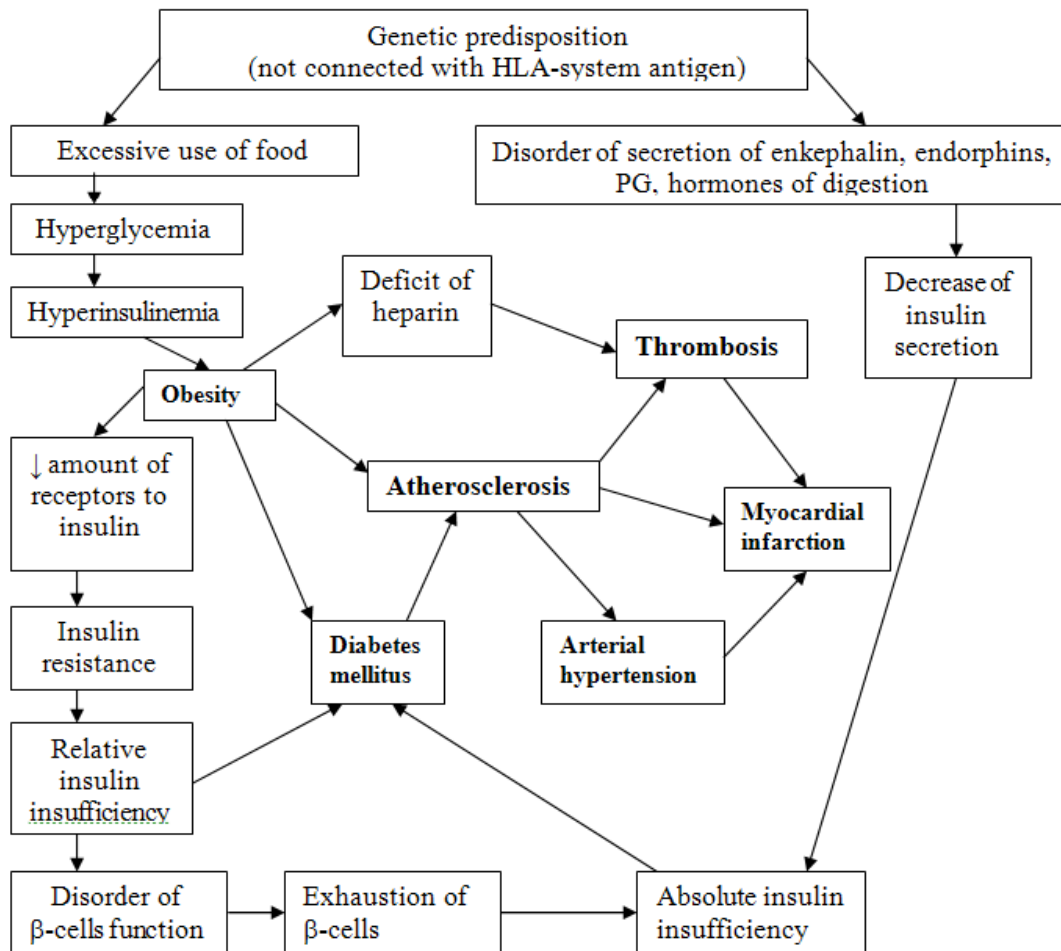
Atherosclerosis:

- rupture, ulceration, hemorrhage, superimposed formation (with total or partial occlusion of the arteries cutting off the blood supply, and resulting in infarction, e.g., acute myocardial ifarction)
- thromboembolism
- aneurismal dilation (due to arterial wall weakening).

Impairments of intermediate metabolism and deposit in adipose tissue

Impairments of intermediate lipid metabolism lead to ketosis, which shows up the increase of level of ketone bodies. It is organic compounds, intermediate products not only fatty but also carbohydrate and albuminous metabolism. Ketone bodies (acetoacetic acid [diacetic], hydroxybutyric acid, acetone) are synthesized in a liver from acetyl-KoA, which appears: a) at oxidizing of fat acids b) at oxidizing pyruvate in the process of exchange of glucose, c) from the row of ketogenic aminoacid (leucine, phenylalanine, tyrosine, tryptophan and other).

Obesity



Obesity is an excessive accumulation of lipids in the adipose tissue.

Obesity is an actual modern problem not from the point of view of aesthetics, but as a risk factor of the development of such pathological processes as diabetes mellitus, atherosclerosis, arterial hypertension and thrombosis. It becomes clear that obesity relates with many diseases and premature aging.

Body mass index (BMI) = (weight in kg)/(height in m)²

BMI	Classification	Disease Risk	Possible Occurring Diseases
Below 16.5	Severely underweight		Anorexia, bulimia, osteoporosis and break down of muscle mass, etc.
16.5-18.5	Underweight		Digestive problems, weakness, chronic fatigue, stress, anxiety reproductive/hormonal dysfunction
18.5-24.9	Normal	Normal	Normal menstruation, can handle stress, good energy levels, vitality, resistance to illness, good physical condition, etc.
25-29.9	Overweight	Increased	Fatigue, digestive problems, circulation problems, varicose veins, etc.
30 - 34.9	Obese (Obesity Class 1)	High	Diabetes, hypertension, cardiovascular diseases, blood clots, strokes, joint problems / arthritis in knees, spine, etc.
35-39.9	Highly Obese (Obesity Class 2)	Very High	Diabetes, cancer, angina, heart attacks, phlebitis, arterial sclerosis and strokes, etc.
40+	Extremely Obese (Obesity Class 3)	Extremely High	Maximum risk of diabetes, cancer, heart disease, premature death.

Types:

By etiology:

- acquired (secondary, symptomatic)

- constitutional (primary)

By pathogenesis:

- alimentary
- metabolic.
- endocrine
- cerebral (cortical).
- hypothalamic

Pathomorphological classification (based on a size and quantity of adipocytes):

- hypertrophic depends on the quantity of fat in each adipocyte that is connected with increased concentration of insulin, hyperlipemia, and decreased tolerance to glucose. Frequently this form of obesity is complicated by development of atherosclerosis and diabetes mellitus at young age.
- hyperplastic. is connected with increase of adipocyte quantity, which depends on the genetic factors or the environmental ones, regulating the adipose tissue morphogenesis in embryo and at early age.

Accumulation of fats in the non-lipid tissues (parenchymatous organs - liver and myocardium) is called the ***lipid decomposition (degeneration)***.

Etiology:

Etiological factors:

- exogenous:
 - overeating, mother's nutrition in pregnancy, child feeding in early childhood, family and national traditions, way of life, the level of wealthy and accessibility of food
 - chronic stress usually changes a behavior of men as to the nourishment and provokes overeating
 - hypodynamia
 - endogenous (nervous and endocrine systems disorder, suppressed catabolism)
 - acquired
 - genetic

Genetic factors (peculiarities of metabolism, activity of enzymes) refer to endogenous ones as well. A peculiarity of obesity etiology consists in the fact, that lipomatous constitution plays a role of a crucial condition.

Pathogenesis:

Obesity is a result of energy disbalance between its production and use.

Three basic pathogenetic mechanisms are important in obesity pathogenesis:

- Increased intake of a food, which does not correspond to the energy expenditures;
- Decreased mobilization of fat from the depots, as a source of energy;
- Excessive fat formation from carbohydrates.

Dysregulative obesity is related to violation of mobilization of fat from fatty depots and activating of lipogenesis, that is possible if presence violation of the neuron-hormonal adjusting of these processes, in particular:

1) Violation of function of **hypothalamus**. Thus it shows brake influence on the ventrolateralis nucleus of hypothalamus - nucleus of "hunger" or ventromedial nucleus – nucleus of "satiety"

2) A decline of tone of the sympathetic nervous system and increasing of tone of the parasympathetic nervous system which is accompanied: a) diminishing of maintenance of catecholamines and oppressing lypolysis) multiplying the secretion of insulin and activating of lipogenesis. Such phenomenon takes place at the deficit of negative emotions, protracted sleep.

3) Hyperproducts of corticotrophin (illness) and glucocorticoids (Kushing's syndrome), when obesity develops after the following mechanism: corticotrophin → glucocorticoids → gluconeogenesis and glycogenolysis → hyperglycemia → hyperinsulinemia → lipogenesis (glucose transformed into fats).

4) Decline of functions of thyroid and sexual glands, when development of obesity is related to the decline of basic exchange and oppressing mobilization of fat from fatty depots.

Metabolic (genetic) obesity is caused:

1) increase ability to convert carbohydrates into fats (more than 50%), that is predetermined high activity of genes which encode the synthesis of enzymes of glycolysis and pentose-phosphate pathway. Glucose is the source of acetyl-KoA, which fat acids are synthesized from. Fats appear at co-operation of glycerin and fat acids. At this time in an organism there is hypoglycemia which is reason of excitation of ventrolateral nucleus of hypothalamus - nucleus of hunger – there is polyphagia.

2) Inherited diminishing of synthesis by adipocytes leptins – regulator of appetite which is accompanied it acute increase.

Syndrome X (metabolic X syndrome)

- insulin resistance
- compensatory hyperinsulinemia
- visceral obesity
- dyslipidemia (□ LDL, □ TG, □ HDL)
- systemic hypertension
- Increased probability of DM-type 2 development

Antiphospholipid syndrome

The antiphospholipid syndrome (APS) is characterized by the occurrence of venous or arterial thrombosis or of specific pregnancy morbidity, in the presence of laboratory evidence of antiphospholipid antibodies (aPL).

The antiphospholipid **antibodies** are:

- lupus anticoagulant;
- antibodies to cardiolipin;
- β 2-glycoprotein-1-cofactor-dependent antibodies that suppress the activity of natural β 2-glycoprotein-1.

Clinical types of APS :

1. Secondary APS associated with SLE and other diseases, especially systemic
2. Secondary APS patients with lupus manifestations
3. Primary APS
4. "Catastrophic" APS (acute disseminated coagulopathy / vasculopathy) with acute multiple organ thrombosis
5. Other microangiopathic syndromes (thrombotic, thrombocytopenic purpura / hemolytic-uremic syndrome), HELLP- syndrome a pregnancy in combination with hemolysis , elevated liver enzymes , thrombocytopenia) , DICS, hypoprothrombic syndrome
6. "Seronegative " APS.

Based on the most recent criteria, classification with APS requires one clinical and one laboratory manifestation:

Clinical:

- A documented episode of arterial, venous, or small vessel thrombosis — other than superficial venous thrombosis — in any tissue or organ by objective validated criteria with no significant evidence of inflammation in the vessel wall, and/or
- 1 or more unexplained deaths of a morphologically normal fetus (documented by ultrasound or direct examination of the fetus) at or beyond the 10th week of gestation and/or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded or at least 1 premature birth of a morphologically normal neonate before the 34th week of gestation due to eclampsia or severe pre-eclampsia according to standard definitions, or recognized features of placental insufficiency

Laboratory:

- Anti-cardiolipin IgG and/or IgM measured by standardized, non-cofactor dependent ELISA on 2 or more occasions, not less than 12 weeks apart; medium or high titre (i.e., > 40 GPL or MPL, or > the 99th percentile) and/or

- Anti- β_2 glycoprotein I IgG and/or IgM measured by standardized ELISA on 2 or more occasions, not less than 12 weeks apart; medium or high titre (> the 99th percentile) and/or
- Lupus anticoagulant detected on 2 occasions not less than 12 weeks apart according to the guidelines of the International Society of Thrombosis and Hemostasis.

Questions for self-control of knowledge:

1. What are etiology and pathogenesis of DM type 1 and DM type 2?
2. What are clinical symptoms and laboratory criteria for diabetes? Explain their pathogenesis.
3. Why in condition of increasing lipolysis people with diabetes may be obese?
4. What are pathogenesis and clinical manifestations of main emergencies in DM? Give a comparative description ketoacidotic and hypoglycemic coma.
5. What are pathogenetic basis of chronic complications of diabetes?
6. What are principles of pathogenetic therapy of diabetes?
7. What is role of fats in body?
8. What is role of hypothalamus in pathogenesis of alimentary-constitutional and hypothalamic obesity?
9. What is role of obesity as an etiologic factor for DM type 2?
10. Specify the biological role of LCAT-traps. Describe mechanism of the process.
11. Which diseases there are manifestations by AFLS. What is antibodies anti-PL repertoire?
12. What are "new" risk factors for atherosclerosis (thrombogenic and inflammatory)?
13. What is role of immune mechanisms in formation and destabilization of atherosclerotic plaques?
14. What is a modified LP? What are features of their structure, causes appearance in body and its role in atherogenesis?

Tasks for self-managed student work:

1. Antiphospholipid syndrome (Hughes syndrome).
2. Disorders of carbohydrate metabolism in hereditary enzymopathies.
3. Pathophysiological basis of obesity.
4. Emergency conditions in diabetes mellitus.
5. Syndrome of insulin resistance

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Basis literature:

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