Atherosclerosis

Methodic materials for international students (IV-VI year)

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Definition:

Atherosclerosis is a chronic disease of elastic and elasticomuscular type of arteries which is characterized by accumulation of atherogenic apoprotein B-containing lypoproteids in intima with further connective tissue development and plaques formation.

Prevalence and clinical significance

Atherosclerosis - associated diseases are one of the most frequent causes of loss of working ability and death in the world. It is the morphological cause of:

- ischemic heart disease
- stroke
- peripheral vascular disease
- aorta aneurism
- vascular disease of the abdominal region (angina abdominalis)
- vasorenal hypertension due to renal arteries atherosclerosis

The highest death rates from coronary heart disease are found in Britain, northern Europe, the United States, Australia, and New Zealand.

The prevalence of the disease is, first of all, determined by risk factors, relating to the lifestyle, but not a race. This is best exemplified by migrants from Japan to Hawaii and in turn to the United States, who adopt the North American lifestyle and then have the same risk of coronary heart disease as those of their host nation.

First morphological signs of atherosclerosis appear even in children, while clinical manifestation of the atherosclerosis-associated disease is usually at age over 40-45

(according to the National Health Examination Survey (USA), IHD, which is associated with atherosclerosis, is the leading cause of death in males even after 35).

THE NORMAL ARTERY. Anatomy, physiology and biochemistry.

An artery consists of three histologically discrete concentric layers. The innermost, luminal part of the artery, the intima, contains a densely adherent monolayer of endothelial cells, bound together by tight junctions, which provide a barrier that strictly controls the entrance of substances to the arterial wall. The endothelial cell layer is adherent to the internal, or basal, elastic lamina, a network of areolar and elastic tissue. This layer is more marked in medium-sized and larger arteries. The media contains vascular smooth muscle cells arranged in a closely adherent monolayer or multiple layers, depending on the size of the artery. Smooth muscle cells secrete a mixture of collagen, elastic tissue, and glycosaminoglycans, which form a dense matrix around them. The adventitia forms the external layer and is separated from the media by an external elastic lamina. It contains a meshwork of collagen and elastic fibrils, smooth muscle cells, and fibroblasts. The adventitia receives its blood supply from a series of externally derived small arteries, the vasa vasora, which also supply the outermost layers of the media. The intima and innermost layer of the media receive their nutritional support from luminal blood.

The media and adventitia together provide a strong, elastic, contractile wall, which provides the physical strength to deal with the hydrodynamic and sheer stress of the pressurized vascular system. It serves to propagate the flow of blood towards the periphery, and to smooth out the pulse as blood reaches small peripheral arteries and capillary beds.

Endothelial cells serve several important metabolic functions. They deter thrombosis and regulate the access of luminal substances and white blood cells to the arterial wall, synthesize compounds that control vascular tone and cell division, and secrete matrix substances from their abluminal surface.

The unbroken endothelial layer protects against thrombosis and maintains normal blood fluidity by a number of constitutive mechanisms.

Endothelial antitrombotic factors:

- heparin (synthesized and secreted on to the luminal surface by endothelial cells; binds and activates antithrombin III)
- thrombomodulin (binds thrombin and activated protein C; activated protein C and protein S serve as potent anticoagulants by innactivating clotting factors Va and VIIIa).
- prostacyclin (product of arachidonic acid; blocks platelet activation and aggregation, and promotes vasodilatation through the suppression of platelet cyclic AMP)
- Nitric oxide (NO); stimulates relaxation of smooth muscle cells, thereby supporting reduced platelet activity. - -

Endothelial cell membrane ADPases reduce local ADP levels and decrease platelet activation at the lumenal surface.

The endothelial cell is freely permeable to water and small hydrophilic molecules. The tight junctions between endothelial cells are impervious to macromolecules. To gain access to the subendothelium, macromolecules, and macromolecular complexes must traverse the cell in vesicles. This rapid, unidirectional process is called transcytosis. It is mediated by specific proteins such as caveolin and N-ethylmaleamide-sensitive factor. Insulin, transferrin, albumin, and low-density lipoprotein (LDL) traverse the endothelial cell by this route, and provide nutrition for arterial wall cells.

White blood cells and platelets do not adhere to normal vascular endothelium. The activation of endothelial cells, platelets, or white blood cells leads to the production of specific sets of adhesion molecules, which promote this. Adhesion molecules are only expressed at very low levels on the normal endothelial cells.

Endothelial cells elaborate the matrix proteins that form the basement membrane on which they lie. They also synthesize a variety of substances that control vascular tone and blood volume, including NO, the endothelins, and angiotensin-converting enzyme, which activates the renin-angiotensin system.

Smooth muscle cells and a few fibroblasts are the only cells in the normal artery wall. Smooth muscle cells provide the tone of the artery wall and elaborate the matrix proteins, which give it its tensile strength and elasticity.

These include collagen, elastin, and glycosaminoglycans.

Aethiology. Risk factors

1. Not reversible
    - age
    - male (especially before 55)
    - genetic factor – positive family history of premature atherosclerosis
2. Reversible

- Cigarette smoking
- Hypertension
- Obesity

3. Potentially or partially reversible
- Hyperlipidemia-hypercholesterolemia (low-density and very low density lipoproteins) and/or hypertriglyceridemia
- Hyperglycemia and diabetus mellitus
- Low level of high-density lipoproteins (HDL)

4. Other possible factors
- Physical inactivity
- Emotional stress and/or personality type

Pathogenesis

I. Dislipidemia.

Cholesterol formation (daily):

300-400 mg of cholesterol – with food

700 mg – synthesis in liver; other organs also participate in cholesterol synthesis (minimum – gut and kidneys)

Cholesterol metabolism (daily):

- 450 mg is used for bile acids
- 450 mg of sterines is excreted with fecalia
- small amount is excreted by sebaceous glands
- small amount is used for hormones' synthesis

Triglycerides (neutral fats) formation takes place in liver and gut.

Lipoproteins: spherical macromolecular particles containing phospholipids, proteins and cholesterol ethers.

5 classes of lipoproteins:

- **chylomicrones** – the biggest ones – carry triglycerides and small amount of cholesterol from gut to blood
- **Very low density lipoproteins (VLDL)**: carry cholesterol, synthesized in liver, to blood

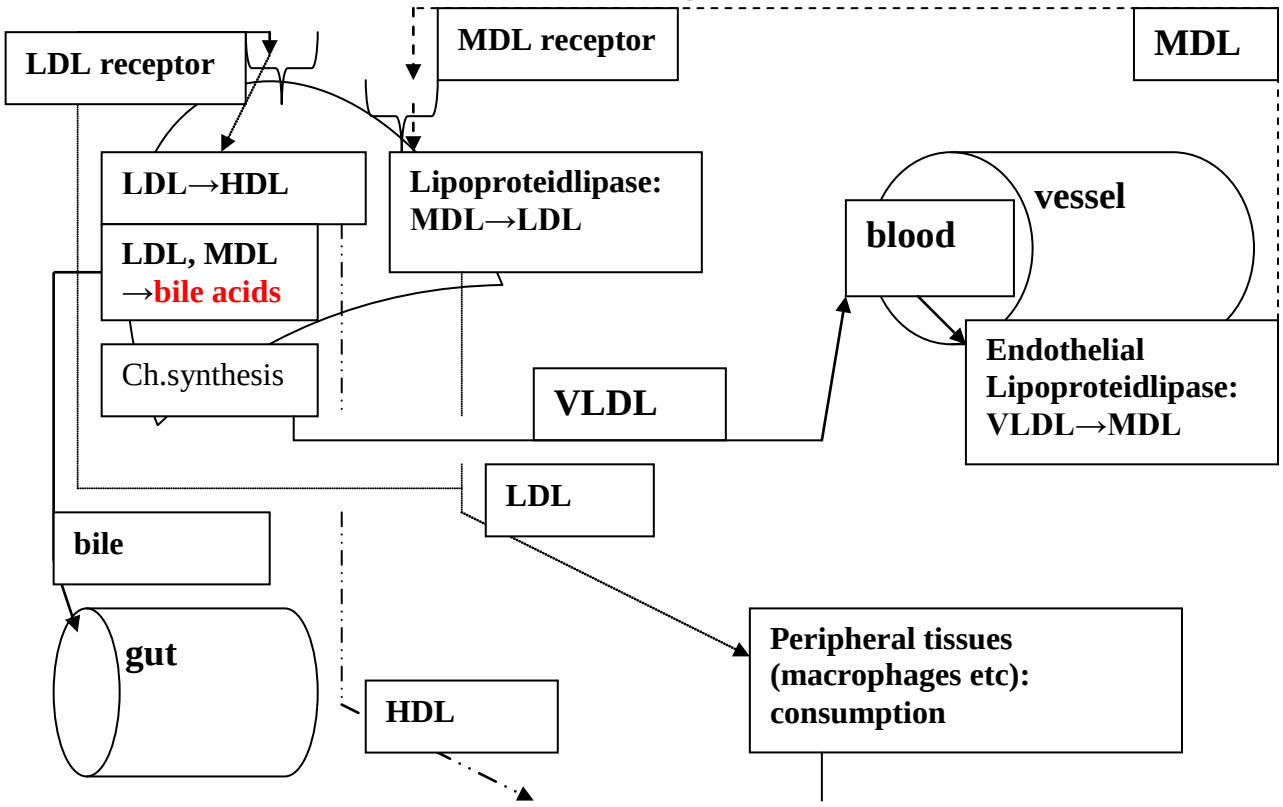
- **Medium density lipoproteins:** are formed in blood: lipoproteidlipase (mostly localized on endothelium) splits VLDL to MDL

- **Low density lipoproteins (LDL):** are formed in liver from MDL (hepatic lipoproteidlipase). Contain maximal cholesterol amount and are mostly atherogenic. They are actively consumed by the cells (liver cells, macrophages and other peripheral cells).

- **High density lipoproteins (HDL):** formed in liver from LDL. Antiatherogenic role: binding of cholesterol in tissues and reverse cholesterol transport (excretion). Also have antioxidant properties.

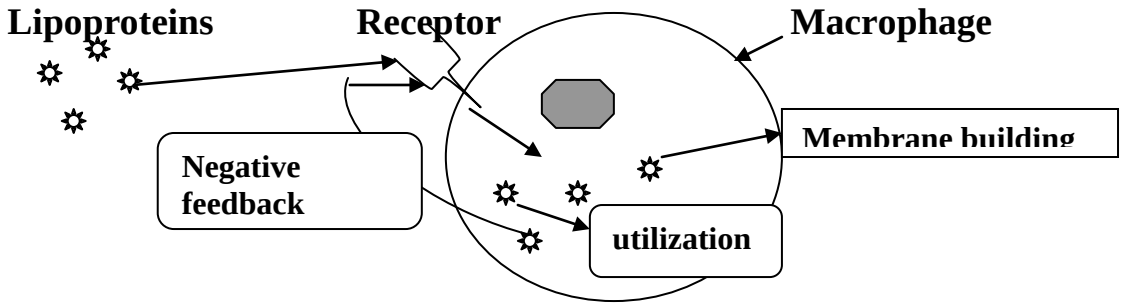
Liver receptors: mediate LDL and MDL consumption by liver cell. Number of receptors is determined genetically; lack of receptors causes some types of hereditary hypercholesterinemia.

As a whole, cholesterol metabolism can be represented at a following scheme



LDL binding in tissues and excretion (reverse transport); antioxidant function

Normal regulation of LDL consumption by macroghages:



Growth of LP concentration in the macrophage leads to stoppage of further LP consumption; remaining cholesterol is used to membranes' building or metabolized by the cell.

Atherogenity coefficient (A.N.Climov):

$$AC = \frac{\text{Total cholesterol} - \text{HDL cholesterol}}{\text{HDL cholesterol}}$$ (normal range – 3 and less)

Apoproteins: glycoprotein sites of lipoproteins (apoA, apoB, apoC, apoD, apoE, apo(a) types). Role: connection with cells receptors, modulation of enzymes' activity (some ones, participating in cholesterol and triglycerides' metabolism and transport). The most atherogenic:

apoB and apo(a) in LDL (because of the genetically determined smallest number of receptors in hepatocytes). Antiatherogenic: apoA (HDL)

Modified lipoproteins: lipoproteins with modified structure (first of all, due to peroxide oxidation – oxidatively damaged). **Atherogenity of modified lipoproteins is higher than that of native ones, because:**

Disturbance of the LP utilization by the macrophages (negative feedback is no more working) ↓ Macrophages are overloaded by LP and transformed to foam cells ↓ Destruction of foam cells lead to deliberation of cholesterol and its ethers and other active substances which go to nearby tissues	**Changes of structure of protein parts of LP** ↓ Appearance of antigenic properties of proteins ↓ Synthesis of specific antibodies ↓ Circulating immune complexes ↓ Affection of endothelium and platelets by immune complexes	**Toxic action against vascular endothelium**
All these factors lead to endothelium affection		

Other factors, affecting endothelium:

- haemodynamic factor (AH)
- role of microorganisms (Chlamidia, H.Pylori, Cytomegaloviruses) in atherosclerosis progression is discussed.
- free radicals (reactive oxygen substances); catecholamines, angiotensin-II influence.
- elevated plasma homocystein level (can be reduced by folic acid 1 mg daily in combination with vitamins B6 and B12 treatment)

The endothelium injury (due to above mentioned factors) leads to:

- increase of LP diffusion from blood to vascular wall
- monocytes and platelets recruitment to the site of injury
- growth of foam cells number in subendothelial layer due to monocytes recruitment, disturbance of normal negative feedback and excessive LP amount in tissues (due to foam cells destruction)
- Destruction of foam cells leads to extracellular cholesterol and its ethers deposition in tissues, so the center (fatty core) of the plaque is formed
- Biologically active substances, deliberated by the affected endothelium, macrophages and adhesing platelets, stimulate smooth muscle cells proliferation and migration to the affected site. Their ability to connective tissue components' synthesis is also stimulated by these substances. This leads to lipid nucleus covering by connective tissue elements, smooth muscular cells and endothelium.

Presence of plaque leads to:

- narrowing of the vessel lumen and development of chronic ischemia of organ (stable forms of stenocardia; atherosclerosis-related cardiosclerosis, causing rhythm disorders and congestive heart failure; chronic brain ischemia etc)
- changes of haemodynamic and appearance of turbulent flows, which lead to trombi formation
- acute conditions, associated with "instable" plaques and tissue necrosis: myocardial infarction, stroke, sudden death etc.

Morphology:

patchy-nodular type of arteriosclerosis with different degrees of affection of different vessels.

Morphological stages:

Stage	Changes	Localization	Age	Symptoms
Early – fatty streaks	Accumulation of lipid-filled smooth muscular cells and foam cells and fibrous tissue in focal areas of the intima; it is believed that they may be reversible.	First of all – aorta Coronary arteries Cerebral arteries	Appear in 10 y.o., occupy 30-50% of aortic surface by the age of 25 Appear at 15 30-40	Asympto-matic
Fibrous plaque (=raised lesions=pear-ly plaques)	Elevated areas of intima thickening; firm, dome-shaped whith an opaque glistening surface bulging into the lumen. Consists of central core of extracellular lipid and necrotic cell debris ("gruel") covered by fibromuscular layer or cap containing large numbers of smooth muscle cells, marcrophages, T-cells and collagen. Cholesterole esters in core may form crystals.	First appear in aorta; than coronary and carotid arteries; than in vertebral and intracranial arteries.	3rd decade with progressive increase with age; appear in men earlier than women;	Asymptoma-tic or chronic ischemia symptoms
Complicated lesions	Plaque calcification, vascularisation, necrosis, thrombosis and ulceration; progressive weakening of artery wall with ruptures of intima, aneurisms formation and haemorrhages; arterial emboli can form when fragments of plaque dislodge into the lumen. Stenosis and		First – 30-39	Chronic ischemia with clinical symptoms (progressive narrowing of the vessel's lumen) Aneurisms and haemorrhages (aorta

	impaired organ function result from gradual occlusion as plaques thicken and trombi form.			aneurism, stroke) Thrombosis and embolisms (infarction, ischemic stroke etc)

High risk of acute complications is in cases when the plaque contains a big lipid core and thin covering. These plaques can be easier ruptured.

Factors, influencing plaque instability and thus complications risk:

- hyperlipidemia
- blood rheology disturbances
- haemodynamic factor (BP fluctuation, angiospastic reactions)

Classifications:

I. Hyperlipidemia types (Frederickson, 1967)

Type	Primary causes	Secondary causes	Plasma cholesterol	LDL cholesterol	Plasma triglycerids	LP disturbances
I	a. lypoproteidlipase deficiency	Systemic lupus erythenmatosus	elevated	Decreased or normal	Elevated	Elevated chylomicrones' level
	b. apoprotein CII deficiency					
IIa	Defect of gene determining LDL receptors synthesis	Hypothyreoidism, exacerbation of liver diseases; nephrotic syndrome	Elevated or normal	Elevated	Normal	Excessive LDL
IIb	Unclear or (in some patients)=IIa	Nephrotic syndrome, Kushing syndrome, neurogenic anorexia	Elevated	Elevated	Elevated	Excessive LDL and VLDL
III	Disturbances of MDL excretion due to apo E (apoE2) defect	Hypothyreoidism, obesity, diabetus mellitus	Elevated	Normal or decreased	Elevated	Excessive MDL and chylomicrones
IV	Unclear	Diabetus mellitus, chronic diseases of kidneys	Elevated or normal	Normal	Elevated	Excessive VLDL
V	Unclear	Diabetus mellitus, alcohol, diuretics, beta-	Elevated	Normal	Elevated	Excessive chylomicrones and VLDL

		blockers, oral contraceptives				

The most frequent are II-a, II-b, IV types; I, III, V are significantly more rare.

The most atherogenic are IIa, IIb, IV types and also lowering of HDL level.

II. Aethiological classification

I. Primary

1) *genetic* (family-related, homo- or heterozygotes)

2) *non-hereditary* - due to the diet and way of life, including alcoholism (which leads to TG elevation)

II. Secondary:

1) *Diabetus mellitus* (I type – TG elevation, II type – total cholesterol, TG elevation, decrease of HDL level)
2) *Hypothyreoidism* (LDL and TG levels elevation)
3) *Primary biliar cyrrhosis or cholestasis due to other causes* (total cholesterole, TG elevation, HDL lowering, appearance of abnormal lypoproteid "X")
4) *Nephrotic syndrome* (total cholesterole, TG elevation, HDL decrease (HDL are excreted with urine). Loss of lipase with urine.
5) *Chronic renal failure, uremia* – TG increase.
6) *Drugs-related: caused by*
   - thiazides
   - beta-blockers (first of all, unselective)
   - glucocorticosteroids
   - androgens, anabolic steroids.

The most severe course: family-related hereditary hyperlipidemia (defect of gene, determining number of LDL receptors on hepatocytes and in cells of vascular wall).

Type	Homozygote	Heterozygote
Number of receptors (% from	0-5%	50%

normal range)		
Age of the disease onset	Early	30-40 years
Cholesterol increase	26 mmol/l and higher	13 mmol/l and less
Cardiovascular symptoms	Early IHD and infarctions, obliterative atherosclerosis	Ischemic symptoms in age 30-40 years old
Other symptoms	Hepatosplenomegalia	

These conditions need active treatment (combined drugs treatment, sorbtion technologies, gene therapy).

Clinical syndromes:

Chronic ischemia (clinical picture depends on localization): IHD, low extremities ischemia, angina abdominalis, chronic cerebral ischemia, vasorenal hypertension

Acute ischemia (thrombosis, embolism): transient ischemic cerebral attacks, ischemic strokes due to trombosis or embolism, myocardial infarction, sudden death (as an acute form of IHD), Lerish syndrome

Aneurismas: aorta aneurism

Lypids accumulation in tissues: xantelasms (around eyes), arcus senilis, xantomas near tendons. These symptoms are relatively rare and appear in patients with hereditary forms or in aged persons.

Vascular wall can be palpated: usually in temporal and radial arteries

Bruits: can be heard above the big vessels (aorta, renal, carotid arteries)

Heart: aortic stenosis (Mencenberg stenosis) may form due to aortic valve calcification or combined stenosis and regurgitation with typical clinical and auscultation picture.

Diagnosis:

Main principles of diagnostic approach:
I. In general

1. Total cholesterol and HDL cholesterol should be investigated in all people over 20 y.o.

2. In case of normal level the investigation should be repeated every 5 years.

3. If total cholesterol is over 6.2 mmol/l (240 mg/dl) lipid spectrum should be investigated and treatment should be started (type of treatment and necessity of drugs use depends on the results of investigation).

II. Investigations in children and young persons should be performed in order to assess possibility of early atherosclerosis development if:

1. severe IIa or IIb or IV types hypercholesterolemia is diagnosed in parents (especially if in one of them there is hereditary form)
2. early appearance (earlier than in age 50 y.o.) of symptoms of any atherosclerosis localization in grandmothers or grandfathers.
3. arterial hypertension detected in child or youth.
4. obesity detected in child or youth.

III. Other diagnostic measurements (both in cases I and II):

1. Life history

- Family and genealogic history (hereditary predisposition to atherosclerosis-related diseases, early onset of atherosclerosis in relatives and localization of changes)
- Nutrition (eats much, prefers sweet or salty food or food with increase cholesterol or saturated fatty acids amount; if possible – content of saturated fats and cholesterol); alcohol intake
- Caloric intake (recent weight gain)
- Drugs intake (ones, producing or aggravating hyperlipidemia): oral contraceptives, estrogens, glucocorticoids, antihypertensives

2. Objective: general signs

- Weight/Height ratio
- Xantomas, xantelasmas, arcus senilis
- Gout tophi (uncontrolled gout may accelerate atherosclerosis progression)
- Recurrent pancreatitis or abdominal pain (primary hyperlipidemia)

- Hepatosplenomegalia (primary hyperlipidemia)

3. Objective: cardiovascular

- signs of AH
- murmurs on aorta
- bruits on vessels

IV. Possibility of following diseases, leading to secondary hyperlipidemia should be taken into attention:

- Uncontrolled diabetus mellitus
- Hypothyroidism
- Uremia
- Nephrotic syndrome
- Obstructive liver disease
- Dysproteinemias (multiple myeloma, lupus erythematosus)

Laboratory diagnosis:

1. Cholesterol blood levels:

Indices	Normal	Borderline	Elevated
Cholesterol	<200 mg/dl <5.2 mmol/l	200-239 mg/dl 5.2-6.2 mmol/l	≥240 mg/dl >6.2 mmol/l
Triglycerids (for TG only: formula to access mg/dl: concentration in mmol/l x 89)	<200 mg/dl <2.26 mmol/l	200-400 mg/dl 2.26-4.52 mmol/l	>400 mg/dl >4.52 mmol/l higher than 1000 mg/dl (11.2 mmol/l) is related to high risk of pancreatitis
VLDL	12-19 mg/dl 0.3-0.5 mmol/l	Higher – elevated	
HDL	1.2-2.0 mmol/l	Lower – decreased; level lower than 0.9 promotes atherosclerosis development	

2. Instrumental diagnosis:

- Ultrasonic examination of vessels (aorta, renal, carotid, vertebral and other arteries) can reveal presence of plaque or (for aorta) presence of aneurisma.

- Intravascular ultrasonic examination also can be used (also for coronary arteries) but the method is costly and invasive.
- The main invasive method that can prove presence of atherosclerotic changes is angiography.

3. Diagnostic formulas (examples):

- Aorta atherosclerosis. Aneurisma of abdominal part.
- Aorta atherosclerosis. Расслаивающая aneurism of the ascendance aorta. Acute aortic valve недостаточность.
- IHD. Stenocardia напряжения III functional class.

Natural history

Fluctuating course of the disease with periods of exacerbations (new plaques formation, accelerated plaques growth, intraplaque haemorrhages, plaque ruptures etc)

Treatment:

1. General approaches

A. Prevention and treatment of atherosclerosis is especially important in following cases:

- IHD
- in relatively young people (below 50 y.o.)
- in cases of positive family history of atherosclerosis-related diseases
- in cases if diabetus mellitus or gout are present, because these diseases are frequent associated with lipid metabolism disorders

B. In all cases of hyperlipoproteidemia (including these when drugs are used) changes of the life style is necessary (diet, physical exercises, weight normalization, smoking cessation, methods of psychological training to prevent and overcome stress).

C. Adequate control of the diseases, accelerating atherosclerosis progression (AH, diabetus mellitus, gout) is obligatory for adequate atherosclerosis treatment. In AH

patients stable SBP and DBP indices should be reached and their fluctuations should be minimal. That can be reached by the use of the prolonged drug forms.

2. Target cholesterol and LP levels in different groups of patients, that should be reached as a result of treatment:

	Without IHD and risk factors	Without IHD, presence of 2 and more risk factors (AH, smoking, diabetus mellitus, family history of cardiovascular diseases)		IHD
		Age over 30	Age below 30	
Total cholesterol mmol/l (mg/dl)	6.2 (240)	5.2 (200)	4.7 (180)	4.0 (150)
LDL cholesterol	<4.1 (160)	<3.4 (130)		<2.6 (100)

2. Cholesterol level and type of treatment

Total cholesterol level	
< 6.5 (250)	Only dietary and lifestyle correction* - 6 months, if ineffective – drug monotherapy
6.5-7.8 (250-300)	Drug monotherapy
>7.8 (300)	Combined drug treatment, sorbtion technologies, surgical treatment (iliac shunt)
Clinical signs independent of cholesterol level	- hypolipidemic treatment (aimed to transformation of the unstable plaque to stable one) - antitrombotic treatment (aspirin, dipiridamol) - surgical reconstruction of the affected vessels and restenoses prevention

* - this type of treatment is used also in cases of higher cholesterol level and/or presence of clinical signs, but in combination with drug and other therapies.

3. Complex diet and lifestyle changing includes:

Measurements	Mechanism of action	Way of use
A. Physical exercises	- Utilization of approx. 500 g of fat	Moderate but regular exercises;

	daily, so alimentary mechanism is minimized **(total cholesterol and LDL lowering)** - stimulation of oxidative processes and thyroid gland function - most of circulating blood go to vessels with maximal vasodilatation potential (muscles, subcutaneous fat), so the influence of hemodynamic factor is minimized From the other side, hypokinesis leads lowering of lypolitic potential of vessels walls, increase of haemodynamic stress and increase of vascular permeability	intensive exercises (systematic or periodical) lead to increase of catecholamines and cholesterol level and atherosclerosis progression
B. Smoking cessation	Smoking leads to: - progression of endothelium injure and thus to atherosclerosis progression - increase of carboxyhemoglobin level and low oxygen delivery to tissues and thus to diminished lysosomal activity in smooth muscle cells and impaired degradation of LDL by smooth muscle cell - hypoxia (see above) leads to smooth muscle cells proliferation	
C. Alcohol cessation	Alcohol intake leads to: - TG level rise and - progression of arterial hypertension and thus to more marked influence of haemodynamic factor on vessels	
D. Diet correction	Following dietary factors lead to atherosclerosis progression: - high amount of cholesterol and saturated fatty acids - high amount of simple carbohydrates (glucose, saccharose etc) – lead to LDL, VLDL, TG levels increase - excess of vitamin D - lack of vitamins B6 and C - peculiarities of electrolytes' contain in food and water	Recommended diet (daily): Cholesterol amount: no more than 250-300 mg Simple carbohydrates – no more than 50 g Total calorage no more than 2000; fats – no more than 30% (10% saturated); carbohydrates – 50%. Fibers are recommended (20-30 g/daily) – bran, special bread with bran etc

Dietary recommendations

Directions	Products recommended
Cholesterol reducing	Meat – beef (300-450 g weekly) or chicken (no more than 200 g daily); other kinds of meat are not recommended Eggs – 2 weekly Milk products – with low cholesterol content. Oils (sunflower, olive etc), containing omega-6-polyunsaturated fatty acids, can be used but they increase total calorage and may lead to gall stones formation
Cargohydrages content changing	Sugar – 2-3 teaspoons daily, honey or fructose can be used instead Porriges: oat and buckwheat. Potatoes – no more than 200 g daily. Grapes, bananas, carrots also should not be used frequently. Soya, rice, tomatoes, cabbage, salad, nuts, apples, cucumbers are recommended.
Use of products with	- fish is recommended 300 g daily, better – salmon, sardines etc, containing omega-3-polyunsaturated fatty acids. These acids lead to

hypolipidemic effect	total cholesterol, LDL. VLDL and TG level lowering as well as decrease tromboxane A2 synthesis and increase of prostacycline synthesis thus demonstrating antiagregant effect. - Food fibers (apples, grapefruits etc) - bran and bran-containing food supplements, enterosorbents - food supplements containing phospholipids and/or polyunsaturated fatty acids: "Liprinol" "Lipostabil" (phospholipids, omega-3- fatty acids – 2 caps x 3 times a day) Fish oil preparations (these in capsels are better tolerated; dosage depends on omega-3- fatty acids content in one capsel) Onion preparations in capsels ("Ilia Rogoff", "Alisat")

If 3 month after beginning of treatment no effect is seen, cholesterol level should be reduced to 200 mg daily and saturated fats – no more than 7% of calorage. If these measurements give no effect in 3 months – drug treatment should be started.

Drug treatment.

Indications – see above.

Main drugs groups

Group	Influence on lipid metabolism	Mechanism of action	Side effects	Doses
Nicotinic acid				
Nicotinic acid	Decrease of LDL, VLDL, TG, LDL fraction associated with apoprotein (a); increase of HDL	Decrease of lypolisis in fat tissue; reducing of cholesterol and TG synthesis in liver	**In case of high doses:** Face hyperemia, flushing, diarrhea, abdominal pain, liver disorders, hyperglycemia, hyperuricemia, supraventricular arrhytmias, sen-sation of burning in urethra during urination. **Contrindications:** gout, diabetus mellitus, peptic ulcer, liver diseases. Levels of glucose, transaminases, bilirubin, uric acid are to be controlled during treatment	High doses are needed (2.0-3.0 g daily – 30-60 tablets, containing 0.05 mg of drug). **Step therapy to improve tolerance:** 1 week – 0.1x3 2 week - 0.2x3 3 week – 0.4x3 4 week – 0.6x3 and up to 1.0x3 **Drug intake directly after meals.**
Endura-cin	Retard preparation of Nicotinic acid		Better tolerated	Up to 1.5 g daily
Acipimox	Nicotinic acid derivate		Better tolerated	Up to 1.0 g daily
II. Bile acids sequestrants				
Cholesti-ramin; cholesti-pol	Better in II a type; Decrease of total choles-terol and LDL (about 15%)	Binding of bile acids in gut, acids are not reabsorbbed and don't return to the liver; choleste-rol is used for new	The most safe drugs, which are not absorbed in gut. Side effects are connected with stomach and gut reaction: - nausea, constipation	Cholestiramin – 16 g daily (8g twice a day, each package contain 4g); 1st day – 4 mg Cholestipol (cholestid)– 20 g dai-

	with mild TG increase; effect – in 1 month	bile acids synthe-sis; increase of LDL receptors on hepatocytes	(diarrhea is more rare) - disturbances of folic acids and vitamins (A,D,E) absorbtion in gut - disturbances of other drugs absorbtion (drug intake 1 hour before or 4 hrs after cholestiramin)	ly (10 mg twice, each package contain 5mg) In drug combinations – decrease of dose up to 8 and 10 g daily respectively; powder can be added to juice, soup etc
Guarem	Decrease of: total cholesterol – 15-20% LDL lowering TG lowering (20-25%); no influence on HDL	Other positive actions: - decrease of appetite -decrease of carbohydrate absorbtion (diabetus mellitus) - желчегон. - positive influence on AH	Minimal: Diarrhea Dyspeptic disorders Rarely – hypoglycemia (control of glucose content in blood)	5g (1 package) x 2-5 times a day with food, containing enough water – milk, soup, juice
Antioxidants				
Probucol (Phenbu-tol)	LDL lowering (10-20%), the effect beco-mes visible 2 month after beginning of treatment but remains 6 months after cessation due to depot in fat tissue HDL lowe-ing (up to 30%)	Antioxidant for LP, reducing LDL modification; improves non-receptor way of LDL consumption by hepatocytes (can be effective in patients with low level of LDL receptors)	Dyspepsia QT increase (can't be used with Amiodarone or in patiens with ventricular arrhytmias) HDL lowering (are not recommended in patients with low HDL level)	2 tab x times a day (1 g daily), better with oil-containing food.
Fibrates				
1 gene-ration – clofibrat (atromid), miscleron are not used; modern – fenofibrat ciprofib-rat, bezafibrat	Decrease of: - total cholesterol (10-50%, less than statins) - VLDL - TG (20-50%) - slight LDL decrease (less than statins) Increase of: HDL Main indica-	Stimulation of lipoproteidlipase, decrease of TG synthesis and increase of HDL synthesis	6-11% Gall stone disease (more often in 1st generation of drugs) **Myosites (combination with statins leads to severe myopathia!!!)** Increase of indirect anticoagulants activity (the dose of anticoagulants should be reduced 30-50%) Cytopenia Increase of hepatic enzymes activity	Gemifibrosil - 0.6x2; 30 min before eating Fenofibrat (Lipantil 200m– retard form) – 0.2 (1 caps) in the evening Ciprofibrat (Lipanor) 0.1 (1 caps) in the evening Bezafibrat non-retard forms 0.2x3 retard-forms 0.4 in the evening

	tion – II b type; also III (to reduce acute pancrea-titis risk); IV, V types			
Statines- the most active hypolipidemic drugs				
Increase of activity: - simva-statin (Zokor) - prava-statin (Lipostat) - Lova-statin (Mevacor) - Fluva-statin (Lescol)	Decrease of: - Total cholesterol - LDL (30-45%) - markedly decrease apoB - VLDL - TG Increase of HDL (slightly -5-8%)	Influence on early stage of cholesterol synthesis – decrease of hydroximethylgluta rilcoenzymA-reductase activity Migration and proliferation of smooth muscle cell reduction (especially simva- and fluvastatin)	3-5%: - increase of hepatic enzymes activity - myopathia - cataracta - sleeping disorders - dyspepsia - allergic reactions **Combination with fibrates may lead to severe myopathia and acure renal failure**	All are retard-forms; whole dose in the evening; cholesterol synthesis is more active at night); Doses (initial and maximal respectively): Lovastatin – 20-80 mg Simvastatin – 10-80 mg Pravastatin – 10-20mg Fluvastatin – 20-40 mg
Statines can be successfully combined with nicotinic acid and bile acids sequestrants.				

Taking into attention the pathogenetic role of elevated plasma homocystein level treatment by folic acid 1 mg daily in combination with vitamins B6 and B12 can be added.

Other methods of treatment:

- Efferent therapy (plasmapheresis, immunosorbtion)
- Partial ileoshunting (Buchvald operation)
- Liver transplantation (in case of homozygote hypercholesterolemia)
- Gene ingeneering methods are now being investigated