ЗМІСТ

Internal Medicine: in 2 books. Book 1. Diseases of the Cardiovascular and Respiratory Systems: textbook

Про книгу

This textbook describes modern data on epidemiology, the concept of etiology and pathogenesis, clinical features, diagnostics, treatment and prevention of diseases of internal organs.

This book combining European experience with current management and healthcare recommendations, adapted to the credit-module system and the principles of evidence-based medicine, is a modern highly informative, professionally oriented publication.

For students, interns, residents, doctor-cadets of higher medical education establishments, physicians, specialists of secondary and tertiary medical care.

Nestor M. SEREDYUK, MD, Professor

TEXTBOOK

Internal Medicine

IN 2 BOOKS

BOOK 1

Diseases of the Cardiovascular and Respiratory Systems

RECOMMENDED
by the Ministry of Health of Ukraine as a textbook for students and interns of higher medical education establishments

RECOMMENDED
by the Academic Board of Ivano-Frankivsk National Medical University as a textbook for students of higher medical education establishments

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Foreword

Profession of the doctor in the field of internal medicine requires regular improvement, which has no limits and exists forever. There are two subjects in a medicine: a patient and a doctor. Country should provide the most comfortable their cooperation (Yu. M. Sirenko, 2016). If in the triangle "patient - doctor - country" a full understanding of the role and place of each part happens, only then an appropriate progress of the society becomes. Internal medicine is the foundation of all clinical medicine. Although many disciplines (infectious, pediatric, skin, neural, occupational diseases etc.) branched out from the internal medicine, but the last one remains the largest field of the clinical medicine. Actually, therapeutic diseases (including cardiac) now occupy more than two-thirds in the structure of mortality in the Ukraine. Meanwhile knowledge of general practitioners, specialists of emergency services, specialists of the various private clinics is not always adequate. We believe, it's due to the lack of qualified educational textbooks.

The authors endeavor, that students and doctors are able to find the necessary information about choosing strategy of treatment (for example, in the cases of acute coronary syndrome, hypertensive crisis, life-threatening arrhythmias, heart blocks, etc.)

Providing by an educational textbook based on the evidence-based medicine is very important in a professionalism of an internist. Actually, such book is in your hands. Recommendation of European societies of internists (ESIM), cardiologists (ESC), arrhythmologists (EHRA), rheumatologists (ILAR), pulmonologists (ERS), gastroenterologists (EAGEN), nephrologists (ERA-EDTA), hematologist (EHA), guidelines of American and Canadian societies (ACC, AHA, ASH, CSC, AMA, ACR, ATS, AGA, ASN, ASH, NYHA) is included. Also, data of BMJ Clinical Evidence, The Cochrane Collaboration, The National Institute for Health and Clinical Excellence, Medscape are taken into consideration as well.

The textbook "Internal medicine" consists of six chapters adapted to appropriate modules (1, 2, 3, 4) forming this subject. Every chapter has identic design: text, applications, black-and-white pictures, color pictures. Information about epidemiology, etiology, pathogenesis, clinical features, diagnostic, treatment, prevention and prognosis is described in all chapters. The applications involve guidelines of European and American medical societies.

Size of the textbook is defined by number of educational plan hours appointed at learning of "Internal medicine" subject (1050 hours including 680 class hours and 370 self-educational hours).

In book presented your attention, the perennial medicinal and educational experience of Department of Internal Medicine of Ivano-Frankivsk National Medical University is considered. This book is equal useful for students of medical universities, interns, residents, and students of faculties of Postgraduate Studies and doctors engaged in self-education and distance medical education.

This book complies with requirements of order of Ministry of Health of Ukraine № 1422 from 29.12.2016 "About amendments to order of Ministry of Health of Ukraine № 751 from 28.09.2012" regarding educational textbooks. According to Article 14-1 of Basis of Legislation of Ukraine concerning Health Care of Ukraine, paragraph 4 of state concerning Ministry of Health of Ukraine approved by decree of Cabinet of Ministers of Ukraine № 267 from 25.03.2015 the new clinical protocols of health care – clinical guidelines are engrained by order of Ministry of Health of Ukraine № 1422 for usage in Ukraine.

We hope that proposed textbook would be interesting and useful for you. We wait for critical estimations, responds, wishes and recommendations.

Sincerely,
N. Seredyuk, I.Vakalyuk, R. Yatsyshyn,
M. Ostrovskyi, V. Seredyuk

Chapter I

DISEASES OF CARDIOVASCULAR SYSTEM

ATHEROSCLEROSIS

The term "atherosclerosis" is derived from the Greek word *athere* that means *gruel* and *skleros* that means *solid, hard.* In 1883, J. Lobstein combined several diseases with morphological changes of the vascular wall and called them "atherosclerosis". Now this group of diseases has three main forms: atherosclerosis, vascular sclerosis of tunica media (arteriosclerosis) and arteriolosclerosis. The term "atherosclerosis" was introduced into medical practice by F. Marchand (1904).

Atherosclerosis is a chronic, focal lesion of arterial walls, which is characterized by accumulation of apoprotein-B-containing lipoproteins and cholesterol in the inner wall of arteries, reactive growth of connective tissue with the formation of fibrous plaques and their subsequent rupture, formation of ulcers, thrombosis, and calcification. Sclerosis and calcification of the muscle type vessels have a better outcome than elastic type.

Academician of AMS of Ukraine D.D. Zerbino (2003, 2005) considered that atherosclerosis is one of the forms of arteriolosclerosis. According to Doerr's classification (1978), four types of arteriolosclerosis are distinguished: 1) Physiological arteriosclerosis (associated with age-related changes of the blood vessels); 2) Arteriosclerosis based on infiltration of arterial wall by lipids; 3) Form of endarteritis arteriosclerosis; 4) Juvenile arteriosclerosis (process progresses due to intense proliferation of the smooth muscle cells with no signs of accumulation of lipids on the vessel walls). Arteriolosclerosis is a lesion of arterioles with impregnation of vascular wall protein substances of plasma (hyalinosis) with further narrowing or even closure of the vessel lumen of the spleen, kidneys and brain.

Epidemiology. Atherosclerosis mainly occurs in people aged of 45—50 years, but early atherosclerotic changes are found in people at the age of 30—35 years and even at 20—25 or even earlier. Atherosclerosis develops in men earlier than in women by 8—10 years. Among the urban population, it is observed more frequently than among rural residents.

Atherosclerosis and its associated complications (coronary heart disease, hypertension, myocardial infarction, and stroke) are the leading cause of increased morbidity and mortality. In Ukraine, the mortality rate due to diseases of the cardiovascular system is 63.4 %. At the same time, in the United States during the last 20 years it's managed to reduce mortality associated with atherosclerosis cardiovascular system by 30 %, by the introduction to practice of national programs to combat with atherosclerosis and hypertension. But in spite of medical progress, atherosclerotic disease remains the most important cause of death in developed nations. In the USA, coronary artery disease is a cause of approximately 1 of every 6 deaths, accounting for more than 400 000 deaths annually.

Risk factors. The most important risk factors for atherosclerosis include hyperlipidemia (total increasement of cholesterol and triacylglycerols in the blood), hypertension, smoking, diabetes, obesity, age, and sex. Less common risk factors involve physical inactivity, family history of premature coronary artery disease, renal failure, hypoalfalipoproteinemia, syndromes of accelerated atherosclerosis, early vascular aging, high fibrinogen level, metabolic syndrome, chronic inflammatory process, and infectious agent. It's proved that the correction of modified risk factors reduces a chance of developing atherosclerosis.

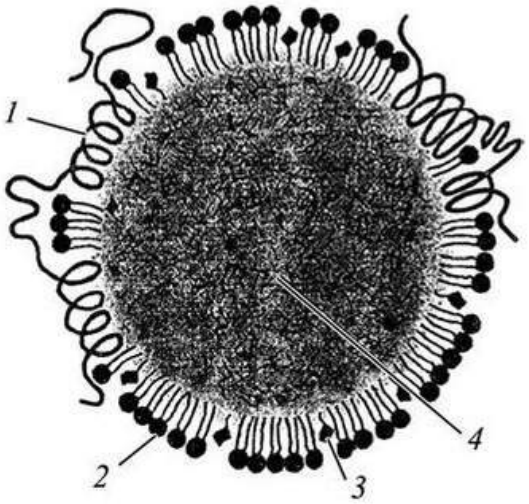


Fig. 1.1. **Lipoproteid structure:**
1 — Apoprotein; *2* — Phospholipids; *3* — Cholesterol; *4* — Core (triacylglicerols, cholesterol esters)

The role of lipid metabolism. Prevalence of disorders of lipid metabolism (dyslipidemia) is very high; it is closely correlated with the incidence of atherosclerosis and coronary artery disease. For example, among men aged of 40—50 years, living in economically developed countries of Western Europe, increasement of total cholesterol level in plasma occurs in 45—57 %. The main plasma lipids are free (non-esterified) fatty acids, triacylglycerols, phospholipids, and cholesterol esters. Lipids in the blood bind to proteins and form complexes — lipoproteins (fig. 1.1).

Non-esterified fatty acids bind to albumin; all other lipids bind to A- and B-globulins. Lipoproteins are the transport forms of lipids; they provide transport of lipids of exogenous (foodborne) origin and lipids that are synthesized by the liver and the small intestine walls (endogenous lipids). Some lipoproteins (high density lipoproteins — HDL) carry out the excess of cholesterol from the cells of peripheral tissues to the liver, where they are oxidized to bile acids.

Proteins of lipoprotein complexes are called apoproteins (or "apo"). Plasma lipoproteins consist of the nucleus containing triacylglycerols and esters of cholesterol and the membrane, which consists of phospholipids, cholesterol, non-esterified cholesterol, and apoprotein. Plasma lipoproteins include chylomicrons: the very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL).

Classification of levels of total cholesterol, LDL and HDL cholesterol, and triacylglycerols (see colour fig. 1.2):

- Total cholesterol (mmol/L):

< 5.2 — optimal;
5.2-6.1 — extremely elevated (boundary);
> 6.2 — high.

- LDL cholesterol (mmol/L):

< 2.6 — optimal (≤ 1.8 — target value);
2.6—3.3 — higher than optimal;
3.4—4.0 — extremely elevated (boundary);
4.1—4.8 — high;
> 4.9 — very high.

- HDL cholesterol (mmol/L):

< 1.0 — low;

1.1—1.5 — normal,
> 1.6 — high.
• Triacylglycerols (mmol/L):
< 1.7 — normal range — low risk;
1.7—2.25 — slightly above normal;
2.26—5.65 — moderate risk,
> 5.65 — very high level — high risk.
• β-Lipoproteins (mmol/L):
< 6000 — normal,
> 6000 — increased.

Chylomicrons are formed in the intestinal walls during absorption of fat food; they transport exogenous triacylglycerols to the place of their disposal (cardiac and skeletal muscles, breasts etc.). In the protein part of chylomicrons (in small quantities) and apoproteins of all major groups — A, B, C, and E are found. Daily chylomicrons transfer from 70 g to 150 g of exogenous triacylglycerols. The VLDLs are synthesized mainly in the liver and are the transport form of endogenous triacylglycerols. They carry out daily about 25—50 g of triacylglycerols synthesized in the liver. Therefore, they are able to move in the electric field (chylomicrons are always "at the start", because they have low level of protein). The main proteins in VLDL are apo-B and apo-C.

The LDLs represent half of all human plasma lipoproteins; they are the main transport form of cholesterol. The content of apo-B-100 in LDL is 95—98 %; there are only 2.5 % of apo-C (I, II) and apo-E proteins. LDL is the end product of metabolic transformation of VLDL, which occurs mostly in the bloodstream under the influence of lipoprotein lipase. The composition of LDL shows that they are formed during hydrolysis of triacylglycerols in the presence of lipoprotein lipase. Recently, there is evidence of the possibility of direct secretion of LDL particles by the liver. The main function of the LDL is to transport cholesterol to the peripheral organs and tissues, if the last ones are unable to provide their own cholesterol synthesis. LDL catabolism occurs mainly in the liver, catabolism of others lipoproteins is provided by the cells of peripheral tissues. Therefore, the process of catabolism of cholesterol provides the cholesterol transport to the peripheral tissues, which is necessary for membranes building, steroid and sex hormones synthesis, and bile acids formation. Every cell in the body is able to synthesize cholesterol, but the most of peripheral cells receive the bulk of the cholesterol from LDL, which transport cholesterol from the place of its core synthesis — the liver and intestines, which produce 90 % of the total cholesterol.

The HDLs are lipid-protein complexes, which have the greatest number of proteins and phospholipids (45—55 % and 24—40 % respectively). The protein part is presented by apoproteins of group A (AI, AII), and only 5 % of the total proteins are of apo-C. In clinical practice, as a criterion of blood HDL-C, HDL or α-cholesterol is used (unlike B-LDL-C). The formation of HDL is taken place in hepatocytes, enterocytes and in the bloodstream during the catabolism of chylomicrons and VLDL. The HDLs, opposite to LDL, transport cholesterol in reverse direction — from the peripheral tissues to the liver for further oxidation to bile acids. The ability to bind cholesterol is represented by one of the major HDL apoproteins — apo-AI.

HDLs protect LDLs from their modification, as lipoproteins loose their inherent properties of unmodified lipid and acquire antigenic properties. In general, for diagnosis

the ratio of LDL/HDL is crucial (its normal value is ≤ 3). If this ratio is increased, the formation of modified LDL is faster; if it's decreased — it's slower.

Not so long, influence of proprotein convertase subtilisin/kexin type 9 (PCSK9) on atherosclerosis development was established. PCSK9 is found in many tissues of the human body. PCSK9 can bind to LDL receptor. When LDL-particle binds to LDL receptor, LDL-particle migrates inside the cell, so LDL blood level decreases. If PCSK9 binds to LDL receptor, the last one becomes inactive, and it's unable to get LDL inside the cells. Also, PCSK9 takes part in Na^+ reabsorbtion in the kidney and glucose metabolism. Nowadays, drugs inhibiting PCSK9 are discovered and approved by FDA for lowering LDL blood level.

Modified lipoproteins are formed in the body (in the blood stream, the intercellular space) from normally synthesized and secreted into the blood lipoproteins. Reasons for modification of lipoproteins include free radicals, lipid peroxidation products, increased concentrations of certain metabolites (glucose), and enzymes of different spectrum.

Transport of cholesterol into the cell as part of LDL is performed by receptor-mediated endocytosis (fig. 1.3).

It's shown that endothelial and smooth muscle cells of arteries, lymphocytes, fibroblasts of the skin contain receptors on their surface that are able to bind LDL.

The capture process of modified LDL by monocytes-macrophages is taken place otherwise. They provide unregulated capture of LDL forming the foam cells (fig. 1.4).

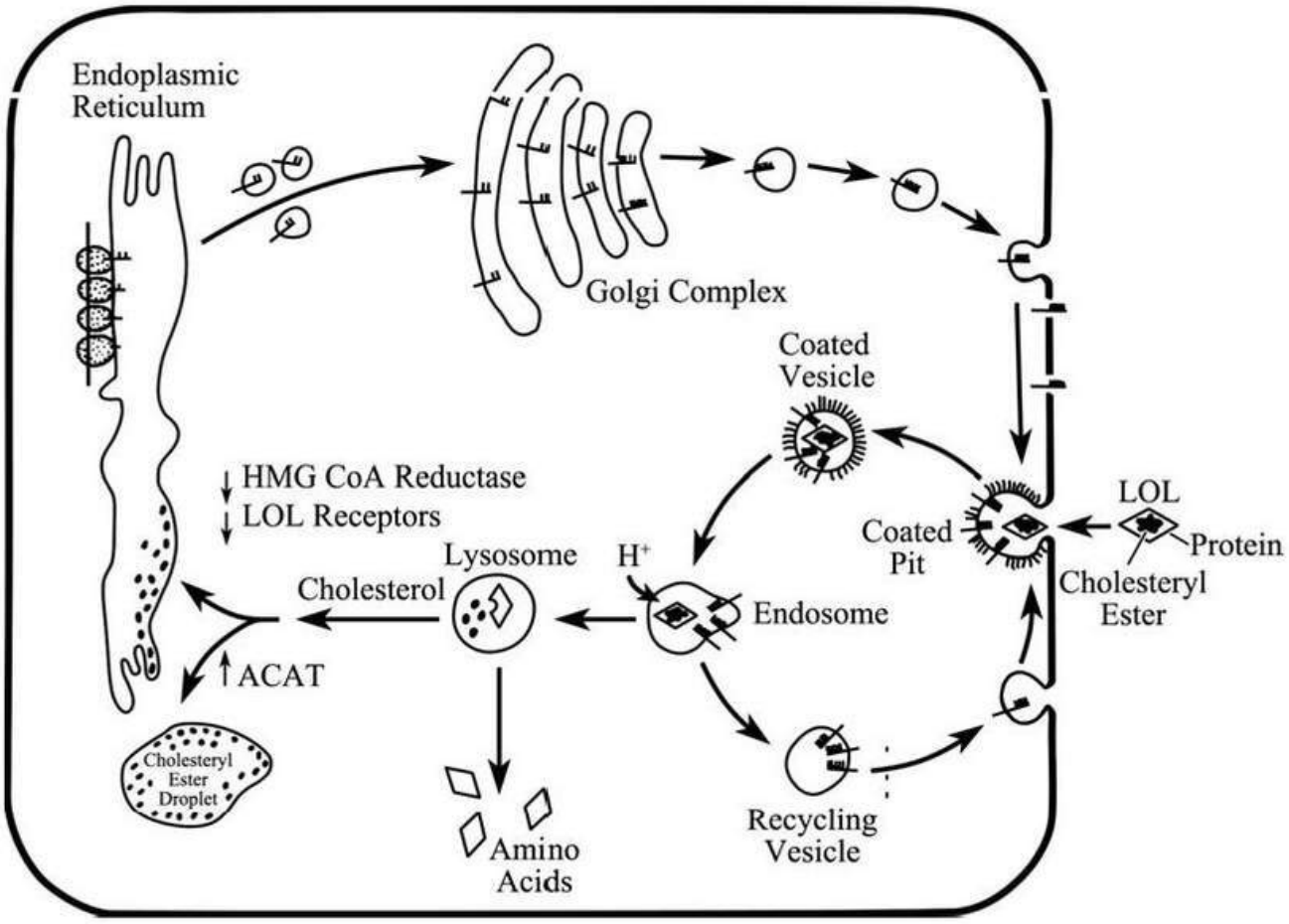


Fig. 1.3. Recepror-mediated lipoprotein capturing. Low dense lipoprotein is captured by the macrophage with the help of specific receptors
(adopted from M. Brown, J. Goldstein, 1984)

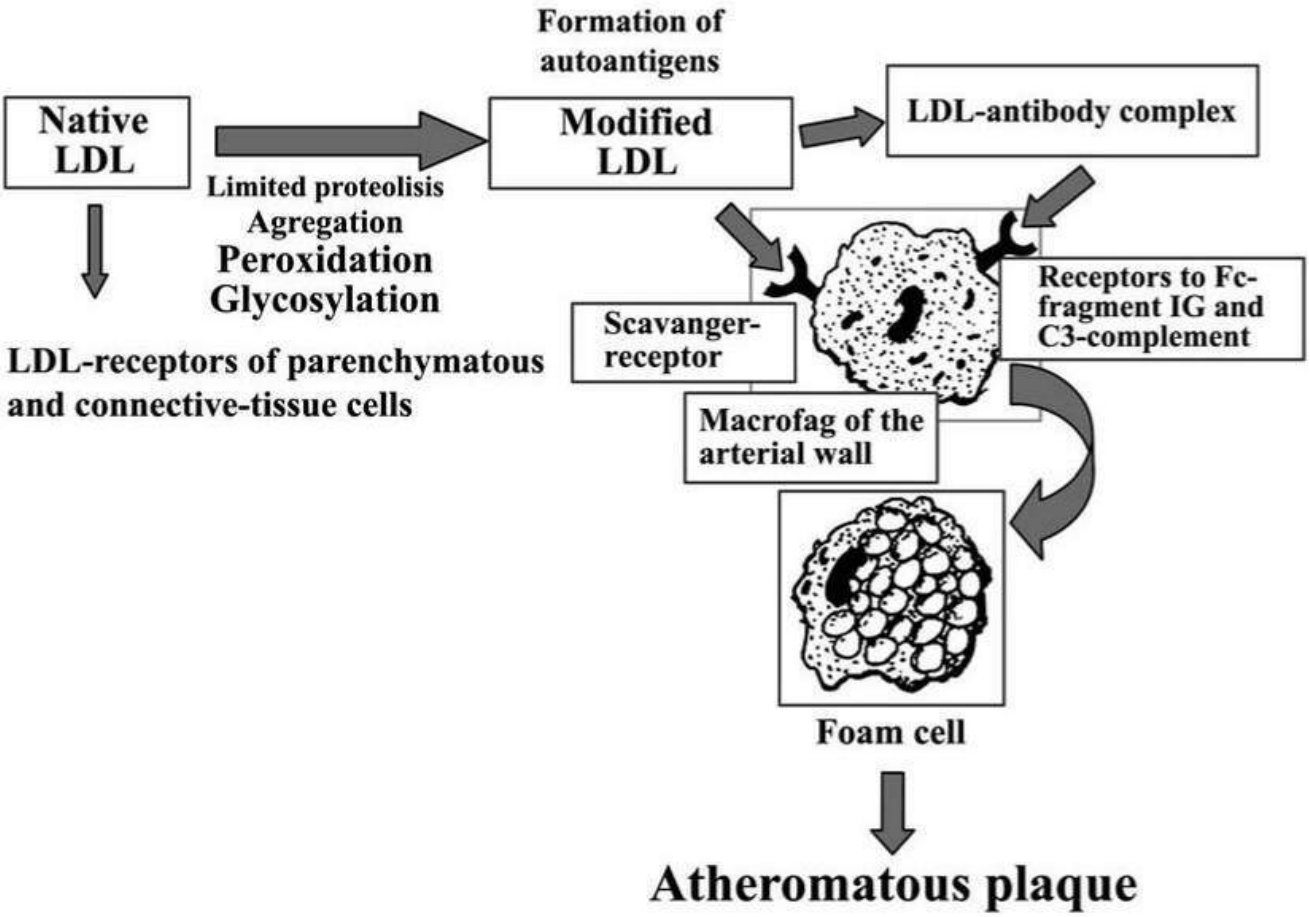


Fig. 1.4. **Modified low dense lipoproteins and immune complexes participation in atherogenesis**
(adopted from A.M. Klymov, N.G. Nikulcheva)

The majority of foam cells die. Herewith cholesterol esters, cholesterol monohydrate crystals are "infused" to the intima. Formed focal accumulations of cholesterol create conditions for the first lipid spots development.

Thus, the foam cells can be seen not only as a precursor cell of atherosclerotic process, but also as a cell-companion.

The migration of monocytes/macrophages to the arterial intima is interpreted as manifestation of the protective function of the reticuloendothelial system created for capture and removal of modified LDL. Macrophages, which performed this function and have been transformed into foam cells, die; it can be viewed as the mechanism that "starts" the atherosclerotic process. As a result of the destruction of monocytes/macrophages, a large number of biologically active substances, including cytokines (IL-1, IL-8, MCP-1-monocyte chemoattractive protein-1) are released; it enhances the migration of monocytes and other lymphocytes into the subendothelial space. A vicious pathological circle occurs (constant recirculation of monocytes to foam cells by the principle "intima — blood").

Thus, the course of atherosclerosis can be represented by the scheme: lipid stain → fibrous plaque → stable atherosclerotic plaque → unstable atherosclerotic plaque (fig. 1.5, fig. 1.6).

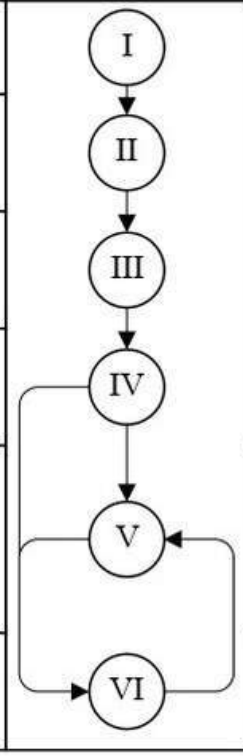
<table>
<tr><th>Nomenclature and main histology</th><th>Sequences in progression</th><th>Main growth mechanism</th><th>Earliest onset</th><th>Clinical correlation</th></tr>
<tr><td>Type I (initial) lesion
isolated macrophage foam cells</td><td rowspan="7"> 
</td><td rowspan="4">Growth mainly by lipid accumulation</td><td rowspan="2">From first decade</td><td rowspan="3">Clinically silent</td></tr>
<tr><td>Type II (fatty streak) lesion
mainly intracellular lipid accumulation</td></tr>
<tr><td>Type III (intermediate) lesion
Type II changes & small extracellular lipid pools</td><td rowspan="2">From third decade</td></tr>
<tr><td>Type IV (atheroma) lesion
Type II changes & core of extracellular lipid</td><td rowspan="3">Clinically silent or overt</td></tr>
<tr><td>Type V (fibroatheroma) lesion
lipid core & fibrotic layer, or multiple lipid cores & fibrotic layers, or mainly calcific, or mainly fibrotic</td><td>Accelerated smooth muscle and collagen increase</td><td rowspan="2">From fourth decade</td></tr>
<tr><td>Type VI (complicated) lesion
surface defect, hematoma-hemorrhage, thrombus</td><td>Thrombosis, hematoma</td></tr>
</table>

Fig. 1.5. Stages of atherosclerotic changes in vessels
(adopted by ACCF/AHA/AATS/ACR/ASA/SCA/ SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease, 2010)

Lipids spots are formed in different parts of the arteries, but first of all in the aorta, where they can be detected at 10 years old (at this age they occupy 10 %, and at age of 25 — up to 30—50 % of the aorta). At the age of 15 lipid spots appear in the coronary arteries, and in 35—45 years old they can be found in the cerebral arteries. Fibrous tissue is transformed in the shape of capsule surrounding "focus cholesterol" for the purpose of limitation. A fibrous plaque is formed, which comprises cholesterol esters by 20—26 times more and non-esterified cholesterol by 6—7 times more than intact areas. Fibrotic plaques are often covered with sores, which also create the condition for the formation of the blood clot wall. The content of the fibrous plaque can flow into the bloodstream, leading to embolism of the cerebral arteries and other organs. One of complications of fibrous plaque is its calcification (atherocalcification). The foci of calcification occur mainly in the abdominal aorta and mouths of its branches in the coronary arteries.

Different stages of atherosclerotic changes (lipid spots and fibrous plaques) can be often seen in one and the same area as a result of wavy course of atherosclerotic process on phase progression, stabilization and regression. Fibrotic plaques impede blood flow leading to ischemia of organs or tissues. Regarding to the possibility of regression of atherosclerotic process, the attention should be paid to the following: lipid spots as initial morphological manifestations of atherosclerosis may disappear at any age as a result of significant and sustained reduction of cholesterol in the blood.

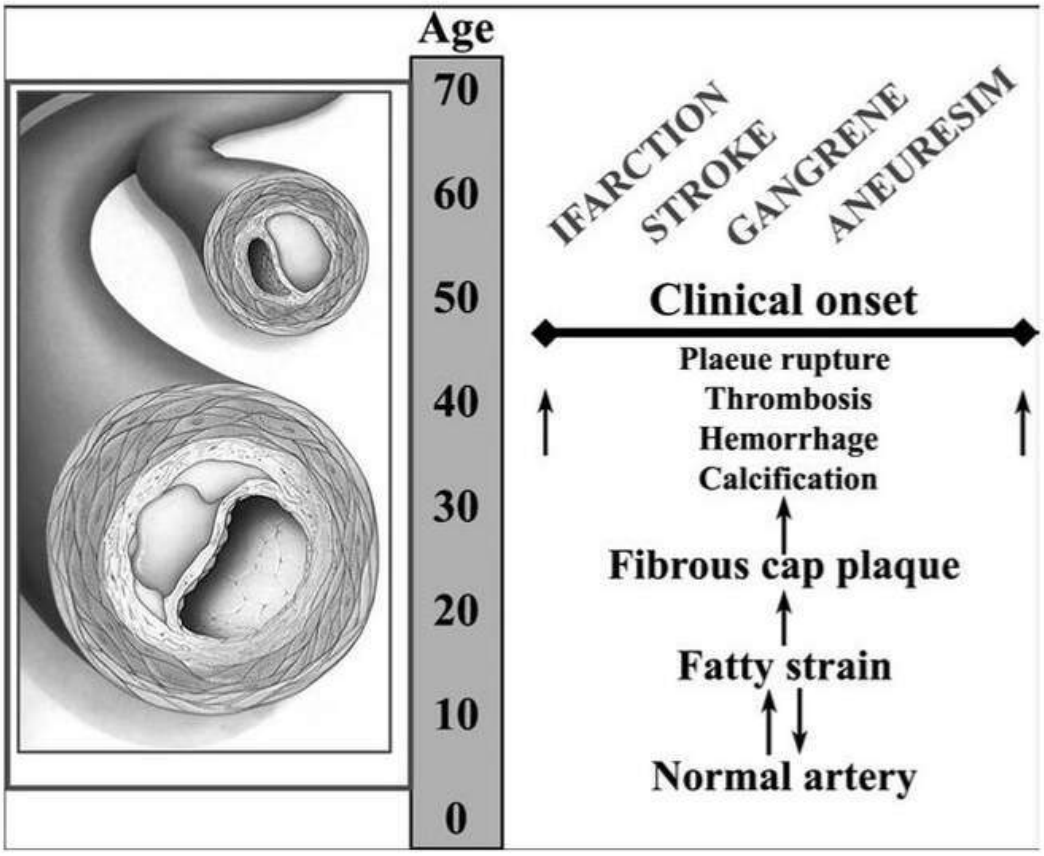


Fig. 1.6. **Atherosclerosis morphogenesis and clinical features**
(adopted from McGill et al, 1963)

The pathological changes of atherosclerotic lesions at the stage of fibrous plaques do not regress. However, in the fibrous plaque lipids can partially or completely disappear, and therefore the plaque may become more flat. It leads to the improved blood circulation through the affected vessel. This phenomenon is called partial regression of atherosclerosis. Macrophages play an important role in lipid removing from the atherosclerotic plaque; they can capture even crystalline cholesterol in the process of phagocytosis. The regression of atherosclerosis is characterized by gradual decrease in foam cells and their disappearance, reduction of necrotic mass in the center of the nucleus plaque. To achieve partial regression, it is necessary to reduce the level of total cholesterol in the blood plasma to the ideal level (3.87—4.13 mmol/L) and to maintain it for 1.5—2 years. Clinical signs of disappearing of lipid fibrous plaques are regression cutaneous xanthomas. There are the following morphological variants of atherosclerotic plaques: 1) Rich in lipids, eccentric; 2) Rich in lipids, concentric; 3) Predominantly fibrous, eccentric; 4) Mainly fibrous, concentric.

It is well known that young (rich in lipids) plaques whith thin cap are located eccentrically; they are most prone to rupture and thrombosis in coronary arteries with subsequent development of unstable angina, STEMI or NSTEMI depending on the degree of obstruction.

There are characteristics of plaques causing fatal thrombosis: 1) They are often located eccentrically; 2) They have nucleus rich in lipid, which occupies more than 50 % of the total plaque; 3) They look like a thin cap (connective tissue capsule, which has smooth muscle cells, but a lot of macrophages — cells of inflammation).

Several complications of atherosclerotic lesion progression may occur, these are: fibroatheroma, thin cap fibroatheroma ("vulnerable plaque") and plaque rupture, necrotic core expansion and risk for the plaque rupture, intraplaque hemorrhage and necrotic core expansion, healed plaque rupture, and erosion. In spite of the fact that the plaque rupture is the most common cause of coronary thrombosis, acute coronary syndromes may occur without it. The plaque erosion is characterized by absence of the endothelium with thickening of intima and minimal inflammatory changes.

The immediate causes of the plaque rupture include: 1) The adverse effects of fluctuations in hemodynamics and coronary artery wall tone, which can be caused by a sudden increase in activity of the sympathetic nervous system (sharp rise of BP, increase in heart rate, coronary flow acceleration); 2) The activity of monocytes/macrophages, which are highlighting metalloproteinases (coagulase, elastase) can "dissolve" cap and cause plaque rupture; 3) Local or generalized vasoconstriction; 4) Thrombosis at the site of injury (ruptured) or even intact plaques due to increased coagulation ability of the blood by increase in platelet adhesion and aggregation, and inhibition of fibrinolysis.

The rupture of atherosclerotic plaque develops mainly in the morning, after waking up, on Mondays, in winter and chill days, and during or immediately after severe emotional or physical stress. There are three options for its further developments:

- Full occlusion of whole lumen of coronary arteries on the background of underdevelopment of distal collaterals leading to STEMI infarction or sudden coronary death;
- Partial occlusion of the coronary artery plus spontaneous thrombosis while collaterals are satisfactorily developed — that promotes NSTEMI;
- Intermittent thrombosis, i.e. "ischemia-reperfusion", manifested clinically as unstable angina.

Thus, there are five types of cells participating in morphogenesis of atherosclerosis: endothelial cells, smooth muscle cells, monocytes/macrophages, platelets, and lymphocytes. The primary substrate for the formation of foam cells is modified ApoB-containing lipoproteins (apo-B-LDL). They are the source of cholesterol for foam cells and atherosclerotic plaque formation.

In addition to cholesterol theory of atherosclerosis, which later had been transformed into the theory of "modified low-density lipoprotein", there is a significant widespread theory of "response to injury". R. Ross (1976) improved R. Virchow's concept. The last one includes: 1) Endothelial damage; 2) Searching for the factors that cause migration of smooth muscle cells through the internal elastic membrane, their proliferation in the intima and migration of monocytes and T-cells in the peripheral blood through endothelial gap between their accumulation in subendothelial space; 3) Synthesis of collagen, elastin and proteoglycans in smooth muscle cells; 4) Intra- and extracellular lipid accumulation; 5) Formation of thrombus. The main causes of endothelial damage include hyperlipidemia, increased stress (mechanical factor), especially in the areas of bifurcation or branching of arterial trunks (contraction of endothelial shear stress as a result); impact of infection (herpes virus, Epstein—Barr virus, cytomegalovirus, Chlamydia, H. pylori infection, etc.) under conditions of chronic immunodeficiency, smoking, exposure to CIC, catecholamines, carbon monoxide, and arterial hypoxemia. Due to the endothelial damage, its desquamation with exposure of thrombogenic subendothelial collagen with subsequent adhesion and aggregation of platelets, release of platelet growth

factor stimulating the migration and proliferation of smooth muscle cells in areas of damage occurs. Chemotactic properties also are present in β-tromboglobulin platelets and thromboxane A_2, which enhance the platelet aggregation and local vasoconstriction.

The theory of "response to injury" was supplemented by immunological concept of G. Wick in 1997. According to it a variety of stress factors including risk factors of atherosclerosis induce endothelial damage and formation of "stress proteins" or "heat shock proteins" (HSP). Expression of HSP is induced by fever, free radicals, mechanical factors, cytokines, and heavy metals. By the immune system HSPs are considered as foreign antigens, which give rise to a true autoimmune reaction. Activation of cooperation between leucocytes is accompanied by the formation of leukotrienes (B4), cytokines, interleukins (IL-1B, IL-8, IL-12, IL-18), C-reactive protein, tumor-necrotic factor alpha, which enhance the proliferation of mature and young thymocytes, stimulate synthesis C-reactive protein (a marker of activity and participant inflammation in atherosclerosis), and killer lymphocyte function (CD56 (NK)). Interpopulation cooperation of leukocytes is activated especially under conditions of hypercholesterolemia and modification of LDL (G.V. Dzyak, 2000). Under these conditions, there is increased formation of anti-NSR65 antibodies that cause lysis of endothelial cells that are affected by the stress factor. It is proved that the titer of antibodies to HSP65 is significantly reduced in patients after percutaneous transluminal coronary angioplasty, after active anti-Helicobacter pylori therapy and treatment of chlamidiosis.

Activation of leukocyte cooperation is accompanied by the formation of pro-inflammatory (pro-atherogenic) cytokines and other inflammatory molecular participants, among which the most important are C-reactive protein, E-selectin, endotoxin, tumor-necrotic factor gamma, interleukins IL-1B, IL-8, IL-12, IL -18, TSD40-TSD154, specific macrophage protein, leukotriene B4, and degradation products of lipo-oxygenase, activated and anti-inflammatory agents, such as IL-4, IL-10, TGF β (transforming growth factor), PD6 (platelet — derived growth factor), and others. The balance between pro-inflammatory and anti-inflammatory factors may be crucial for the progression of atherosclerosis. The most pronounced atherogenic properties have modified lipoproteins. Oxidized low-density lipoproteins (oxLDL) are autoantigens that induce strong local immune response in the plaque. In addition, oxLDL stimulates apoptosis, which takes part in destabilization of the plaque. There are mechanisms of elimination from the body oxLDL:

- Joining them by special receptors of macrophages and phagocytes;
- Joining of antibodies IgM and IgG.

However, the presence of oxLDL correlates with major risk factors for coronary artery disease, these are hyperdipidemia, smoking and diabetes.

Another important factor in atherogenesis is heat shock proteins — HSP (mentioned above), or chaperones, which are cyto-protectors. Heat shock proteins also induce products of antibodies. Immunity against HSP is pro-atherogenic; against oxLDL it is protective. Vaccine-containing antibodies (SgM and SgG) against LDL are developed. Such vaccine causes the "destruction" of LDL.

Dyslipidemia is the most important risk factor of atherosclerosis formation (tables 1.1 and 1.2).

TABLE 1.1

Classification of dyslipidemia and its occurrence

Type	Primary Lipid Elevation	Lipoprotein	Occurrence
I	TG	Chylomicrons	Rare
IIa	C	LDL	Common
IIb	C, TG	LDL, VLDL	Most Common
III	C, TG	LDL	Rare
IV	TG	VLDL	Common
V	TG	VLDL, Chylomicrons	Rare

TABLE 1.2

Classification of dyslipidemia and its atherogenicity

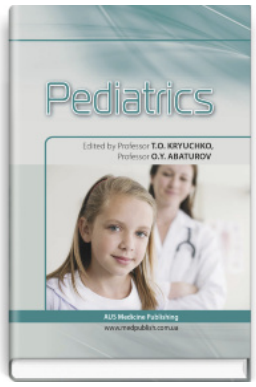
Phenotype	Average of overnight serum	Lipoprotein (s) Elevated	Blood Cholesterol Levels	Blood Triglyceride Levels	Atherogenicity
I	Creamy top layer	Chylomicrons	normal to	↑↑↑↑	none seen
IIa	Clear	LDL	↑↑	Normal	+++
IIb	Clear	LDL & VLDL	↑↑	↑↑	+++
III	Turbid	LDL	↑↑	↑↑↑	+++
IV	Turbid	VLDL	normal to ↑	↑↑	+
V	Creamy top, turbid bottom	VLDL & Chylomicrons	normal to ↑	↑↑↑↑	+

Characteristics of Hyperlipidemia Types and Possible Ways of Their Correction

Family hyperchilomicronemia or type I hyperlipoproteinemia occurs rarely. Clinical signs may appear in childhood, sometimes the first symptoms are found in adults. This type is characterized by a sharp increase of triacylglycerols (from 4.5 to 112.9 mmol/L, while normal value is up to 2.3 mmol/L), which is due to the chylomicrons fraction. After settling the patient's plasma in a refrigerator for 24 hours the creamy layer appears. Signs of this type include the attacks of abdominal colic, pancreatitis, hepatosplenomegaly, and xanthoma of the skin. Atherosclerosis in such persons doesn't develop. Patients with type I hyperlipoproteinemia should be recommended to limit the intake of fat — up to 25—35 g/day (0.5g/kg of body weight) with the same decrease in consumption of saturated and unsaturated fatty acids in the diet. Carbohydrates can be consumed in normal amounts. Proteins shouldn't be limited. Drug correction in this type of hyperlipoproteinemia is ineffective.

Family hyperlipoproteinemia is the type IIa hyperlipoproteinemia. This is the most serious abnormality of lipid metabolism; the risk of CHD in such individuals is by 10—

Рекомендована література



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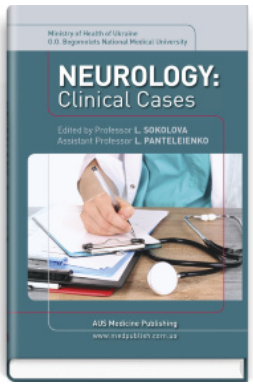

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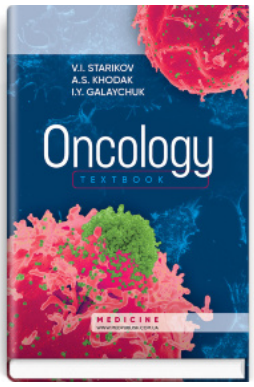

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