Lecturio Medical Knowledge Essentials – Atherosclerosis

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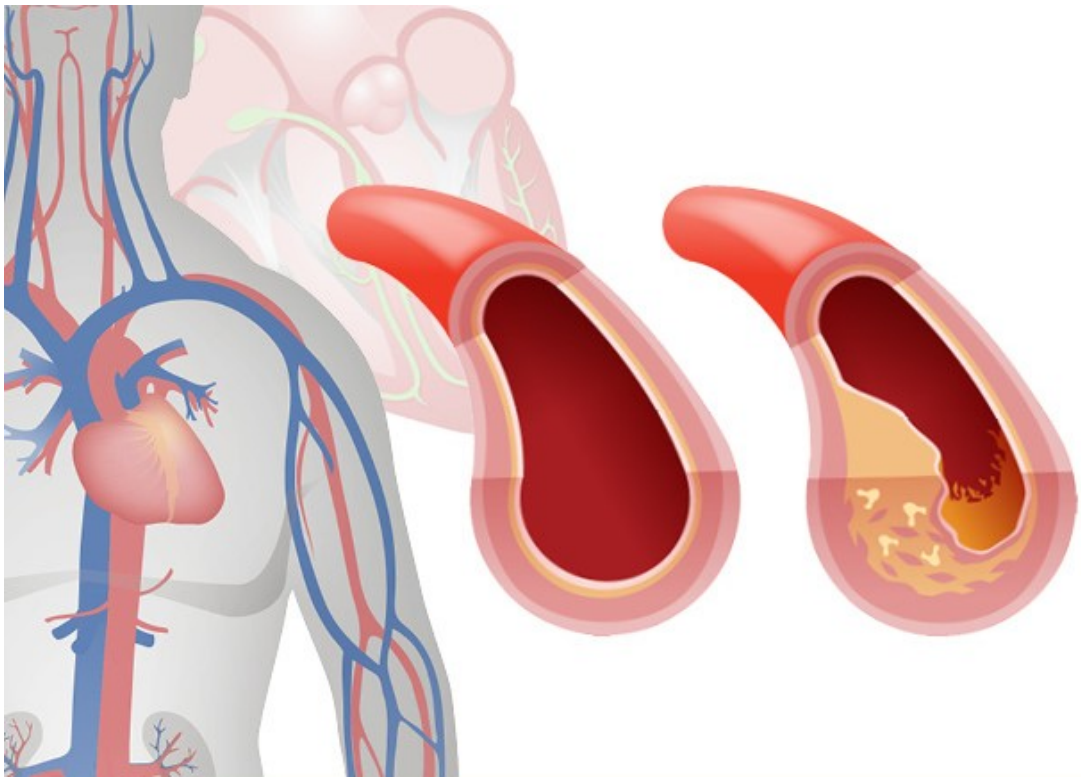

Authors:

Ahmed Elsherif, Suez Canal University; Stanley Oiseth, Chief Medical Editor, Lecturio

Atherosclerosis is the thickening of the arterial wall together with loss of elasticity due to variable pathogenesis. The term atherosclerosis is derived from the Greek words "*athērē*" meaning a substance like hulled grain kernels, or porridge, plus "*sklērōsis*" meaning hardening. The changes in atherosclerosis take place in the intima and media of blood vessel walls and lead to a stiffening of the vessel walls and narrowing of the vascular lumen.

For further review of this topic, including links to video lectures by specialists in the field, follow this link: https://www.lecturio.com/concepts/coronary-heart-disease

Epidemiology

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. Within the USA and EU, atherosclerosis involving the coronary, cerebral, and peripheral arteries accounts for the most morbidity and mortality (approximately 50% of all deaths) than any other disease, with many deaths occurring under 65 years of age.

Etiology

Atherosclerosis is a chronic inflammatory disorder that takes place in the walls of blood vessels. In the process of inflammation, oxidized LDL-cholesterol is involved. Lipids, calcium, and other cellular debris are stored mostly in the intima of large and medium-sized arteries, thereby causing the inflammatory process to cause vessel wall thickening and plaque formation.

Hyperlipidemia, especially hypercholesterolemia, is a major risk factor for atherosclerosis. LDL cholesterol ("bad cholesterol") is the major culprit. It is the lipid-cholesterol-protein complex that delivers cholesterol to peripheral tissues, while high-density lipoprotein (HDL) is the type that mobilizes cholesterol from the periphery (even from atheromas) and transports it to the liver for catabolism and biliary excretion. HDL ("good cholesterol") correlates with reduced risk when it is high; low levels correlate with higher risk. Hypercholesterolemia can be caused by abetalipoproteinemia, lipoprotein lipase, and apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia.

Risk Factors

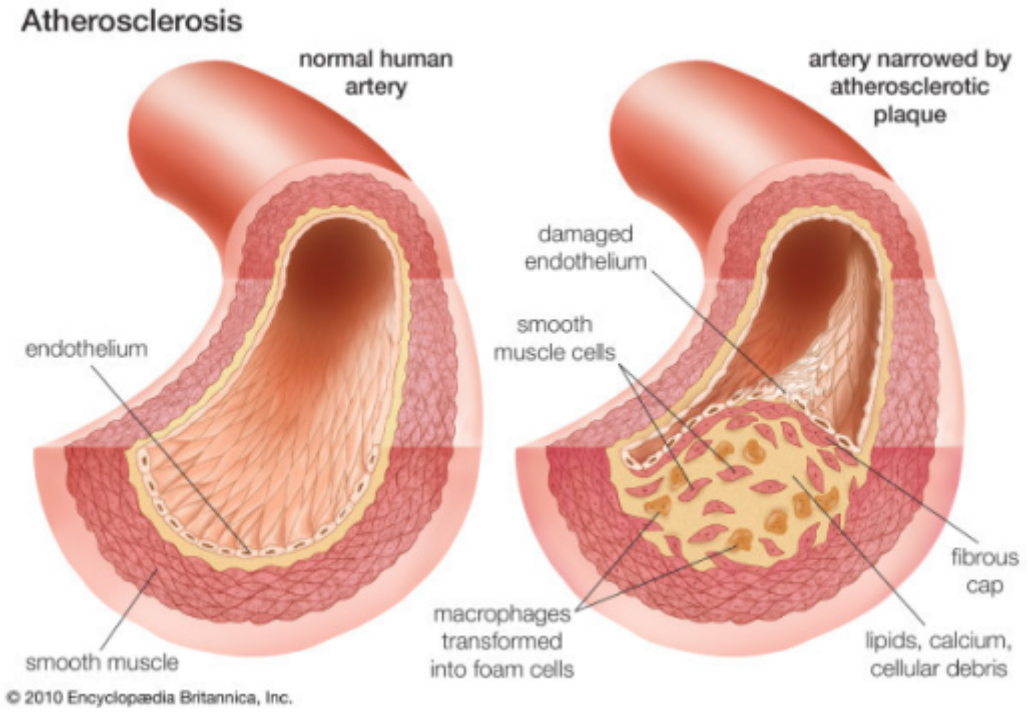

Image: "Coronary atherosclerosis." by Subbotin, V.M. License: CC BY 2.0

The risk factors associated with the development of atherosclerosis are divided into modifiable and nonmodifiable risk factors. Non-modifiable risk factors are male gender, age, genetic abnormalities, and family history. The modifiable risk factors include

hypertension, hyperlipidemia, cigarette smoking, diabetes, and inflammation. The modifiable factors can be subdivided into first and second order risk factors.

First-Order Modifiable Risk Factors

- Cigarette smoking promotes early development and rapid progression of atherosclerosis.
- **Arterial hypertension:** Due to the high-pressure load, endothelium damage occurs faster.
- **Diabetes mellitus:** Increased blood glucose levels cause reactive glycosylation, that itself causes increased phagocytosis and endothelial damage.
- **Hyperlipidemia:** Excessive LDL cholesterol increases the risk of atherosclerosis, especially if HDL cholesterol levels are also low.

Second-Order Modifiable Risk Factors

- Lack of exercise
- Psychological or emotional stress
- Obesity
- Hyperuricemia
- Hypertriglyceridemia
- Fibrinogenemia,
- Hyperhomocysteinemia
- Glucose tolerance disorders
- Chronic renal failure
- Increased lipoprotein (a)

Classification

Macroangiopathy refers to the changes in large and medium-sized arteries, while microangiopathy in hypertension refers to the pathologic changes in the arterioles, which is called arteriolosclerosis, which is one of the four types of arteriosclerosis, the general term for “hardening of the arteries.” The four types of arteriosclerosis are atherosclerosis (the most common), arteriolosclerosis, Mönckeberg medial sclerosis (characterized by calcifications of the medial walls of muscular arteries), and fibromuscular intimal hyperplasia (in muscular arteries larger than arterioles, caused by inflammation or injury)

Hyaline arteriolosclerosis shows homogeneous, pink hyaline thickening of the arterioles due to plasma protein leakage across injured endothelial cells and increased smooth muscle cells (SMCs) in response to hypertension; it leads to narrowing of the lumen and is more severe in diabetes. **Hyperplastic arteriolosclerosis** occurs in severe cases of hypertension; the arterioles show concentric, laminated (“onion-skin”) thickening of the walls due to SMC proliferations and thickened, reduplicated basement membranes; in very severe or malignant hypertension, fibrinoid deposits and vessel wall necrosis (necrotizing arteriolitis) are seen, most notably in the kidney.

The Various Degrees of Severity of Atherosclerosis

Mild	Moderate	Severe

• Endothelium becomes damaged • Factors: high blood pressure, cigarette smoke	• Damage causes an inflammatory response and white blood cells deposit cholesterol forming an atheroma • Calcium salts and fibrous tissue form plaque • Artery loses elasticity and narrows	• Plaque restricts blood flow • High blood pressure • Increased blood pressure promotes the formation of more plaques

Clinical Features

Atherosclerosis can be present for years and decades without any symptoms. Common manifestations include **coronary artery disease, cerebrovascular disease, peripheral artery disease,** and **infrarenal aortic aneurysm**.

High-yield fact:

Metabolic syndrome refers to the presence of at least 3 of the following 5 risk factors:

- Abdominal obesity (waist circumference > 102 cm in men, > 88 cm in women).
- Elevated triglycerides (≥ 150 mg/dL) or drug treatment for elevated triglycerides
- Low HDL cholesterol (< 40 mg/dL in men, and < 50 mg/dL in women) or drug treatment for low HDL cholesterol
- Fasting plasma glucose > 100 mg/dL or drug treatment for elevated blood glucose
- Blood pressure > 130/85 mm Hg or drug treatment for elevated blood pressure

Pathophysiology

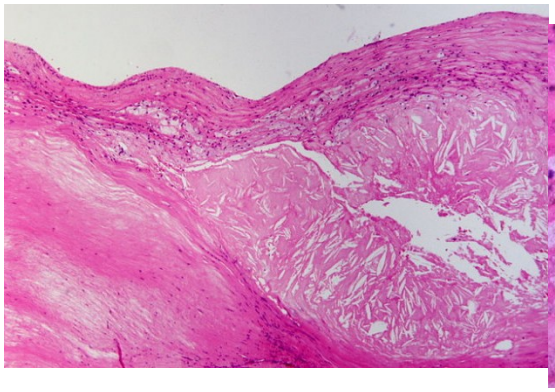

Image: “Atherosclerotic plaque with cholesterol crystal gaps, foam cells and fibrosis. Histology. H&E stain.” by Patho. License: CC BY-SA 3.0

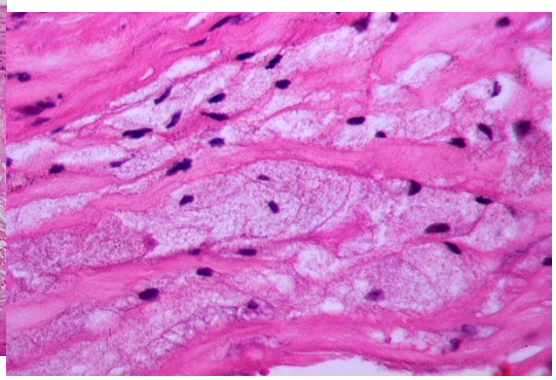

Image: “Foam cells in atherosclerotic plaque. Histology.” by Patho. License: CC BY-SA 3.0

The current view of pathogenesis is called the “response to injury” hypothesis. The **endothelium is first injured and atherosclerosis is the result of chronic inflammatory and healing response of the arterial wall to this injury.** The early and evolving changes involve progression of a complex interaction of modified lipoproteins, macrophages, and T lymphocytes with endothelial cells (ECs) and smooth muscle cells (SMCs) of the arterial wall. In summary, atherosclerosis progresses in the following sequence:

- Endothelial injury and dysfunction, producing increased vascular permeability, leukocyte adhesion, and thrombosis.
- Due to the endothelial injury, nitric oxide (NO) synthesis is disrupted and endothelial dysfunction occurs.
- Accumulation of lipoproteins (mainly LDL and its oxidized forms) in the vessel wall.
- Monocyte adhesion to the endothelium, followed by migration into the intima and transformation into macrophages and foam cells (containing lipid vacuoles)
- Platelet adhesion
- Factor release from activated platelets, macrophages, and vascular wall cells, inducing SMC recruitment
- SMC proliferation, extracellular matrix (ECM) production, and recruitment of T cells
- Lipid accumulation both extracellularly and within cells (macrophages and SMCs)
- Calcification of ECM and necrotic debris late in the pathogenesis.

Initially, LDL cholesterol is deposited in the intima of the vessel wall. It is then oxidized and is followed by a local inflammatory response, i.e., monocytes start migrating into the tissue. After they phagocytize the LDL cholesterol, foam cells containing lipid vacuoles are formed. These early atherosclerotic lesions are referred to as **fatty streaks** and occur especially in areas with high mechanical stress (for example, at the proximal left anterior descending artery (LAD) and at the carotid bifurcation).

Gradually, there is an accumulation of lipids and cellular debris in the intima. Different cells within the vessels walls release mediators, and muscle cells from the tunica media migrate into the intima and proliferate.

The fatty core is surrounded by connective tissue which makes it dense and inaccessible, hence, the stored LDL cholesterol cannot be degraded. These plaques may contain newly-formed vessels originating from the **vasa vasorum** that can cause bleeding into the plaque.

Calcium starts to accumulate in the growing plaque.

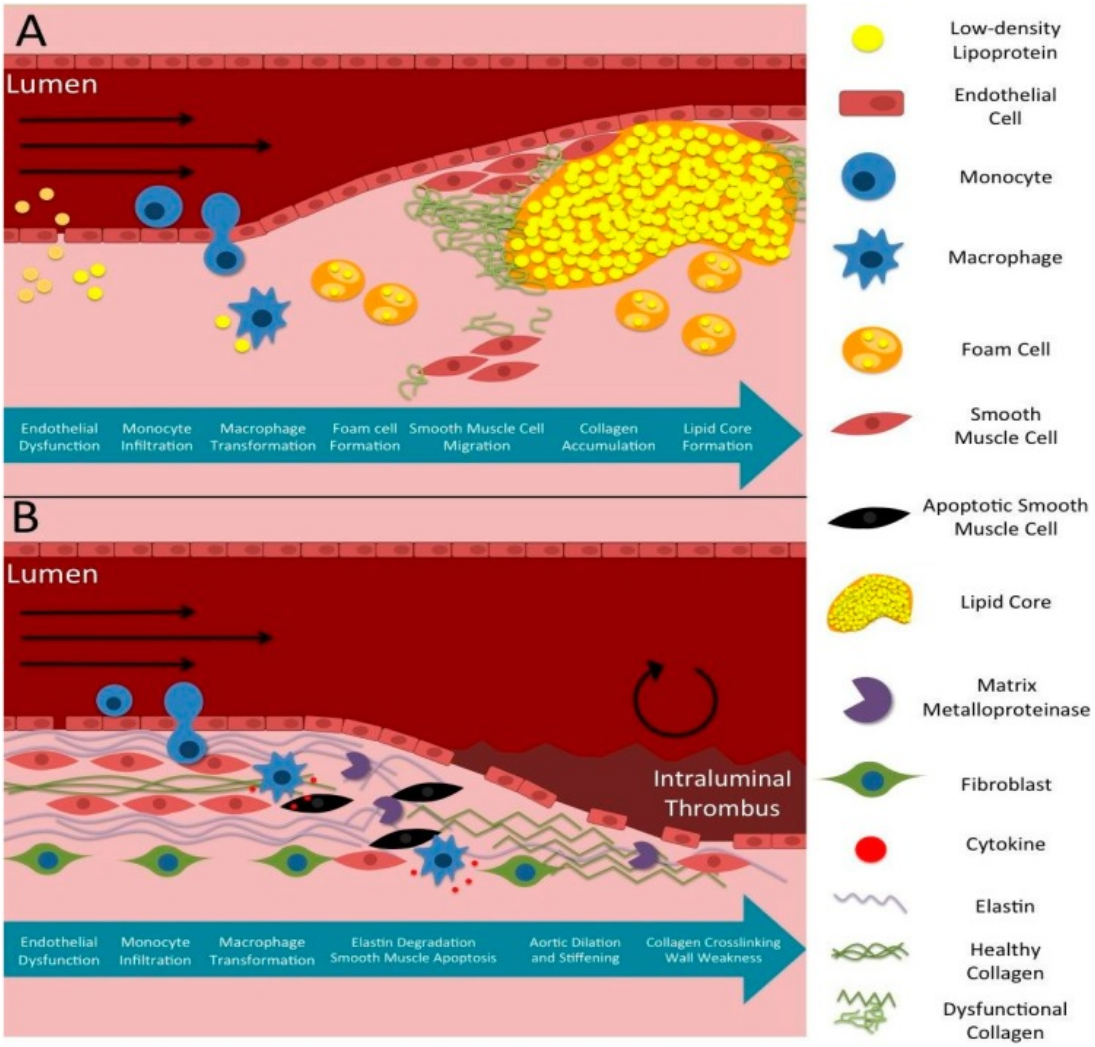

Image: "Typical Disease Progression of Atherosclerotic and Aneurysmal Disease: (A) Chronological atherosclerotic plaque formation starting at endothelial dysfunction and ending in lipid core formation and turbulent, reduced blood flow (B) Chronological aneurysm formation highlighting similar early steps, but resulting in extracellular matrix degradation, vessel expansion, and turbulent flow" by Lin, J.B., et al. License: CC BY 4.0

Plaques that have a large fatty core and only a thin fibrous cap are at risk of rupture, which can lead to such intense activation of the coagulation system that complete thrombotic occlusion of a vessel occurs.

Plaque rupture can also cause cholesterol emboli to migrate to remote blood vessels (for example, to the renal arteries).

Another consequence of atherosclerosis is the formation of an aneurysm mostly caused by extracellular matrix degradation and interference with the vascular supply of the **tunica media**.

Critical stenosis is the degree of occlusion by plaque that is severe enough to cause tissue ischemia, which is 70–75% in the coronary and most other arteries. At this level, the arteries can not dilate sufficiently to supply enough blood when there is an increase in oxygen demand, so that chest pain may occur with exertion, as in stable angina. More severe stenosis leads to more severe imbalance between oxygen demand and supply, leading to the development of more severe ischemic heart disease, including ischemic cardiomyopathy and infarction.

History and Physical Examination of Atherosclerosis

Patient history is taken to identify the risk factors, such as family history. The patient should also be asked about comorbidities, medications, and walking distance tolerance. Physical examination provides information about skin color, temperature, and ulcerations due to circulatory disorders if they are present. The heart should be auscultated. ECG or stress ECG can be helpful.

Laboratory Tests

Lipid profile consisting of total cholesterol, LDL and HDL cholesterol, triglycerides, lipoprotein (a), and homocysteine should be done. If myocardial infarction is suspected, cardiac enzymes, such as troponins, CK and CK-MB, GOT, LDH, and myoglobin tests must be done.

Inflammatory markers such as CRP should also be investigated. Markers of glucose metabolism, such as fasting blood glucose and HbA1c should also be analyzed. Other tests include:

- Complete blood count
- Sodium and potassium
- Coagulation parameters
- TSH
- Creatinine
- Rheumatoid factors

Diagnostic Imaging

Sonography

Doppler sonography offers a good, non-invasive way to take a better look at the vessels. It is used for both closure and perfusion measurement and the determination of the **ankle-brachial index,** as well as for measurement of the flow velocity pulses.

Color duplex sonography combines two methods and allows the examination of **vessel** sections and gives a color code depending on the blood flow. Intravascular ultrasound (IVUS) can be used for the assessment of **coronary arteries.**

An echocardiogram can be done for the assessment of structural or functional abnormalities of the heart. Ejection fraction and the contractility of the heart are 2 important functional parameters that can be assessed using an ECG.

Angiography

CT and MR angiography also offer the advantage of non-invasive diagnostics over conventional angiography because of the better detail provided, with 3-D reconstruction possible for precise treatment planning. CT angiography offers a rapid assessment especially in emergency diagnosis, whereas MR angiography has the advantage of low radiation exposure.

Conventional angiography, however, has the advantage of simultaneous intervention

options (such as stent angioplasty).

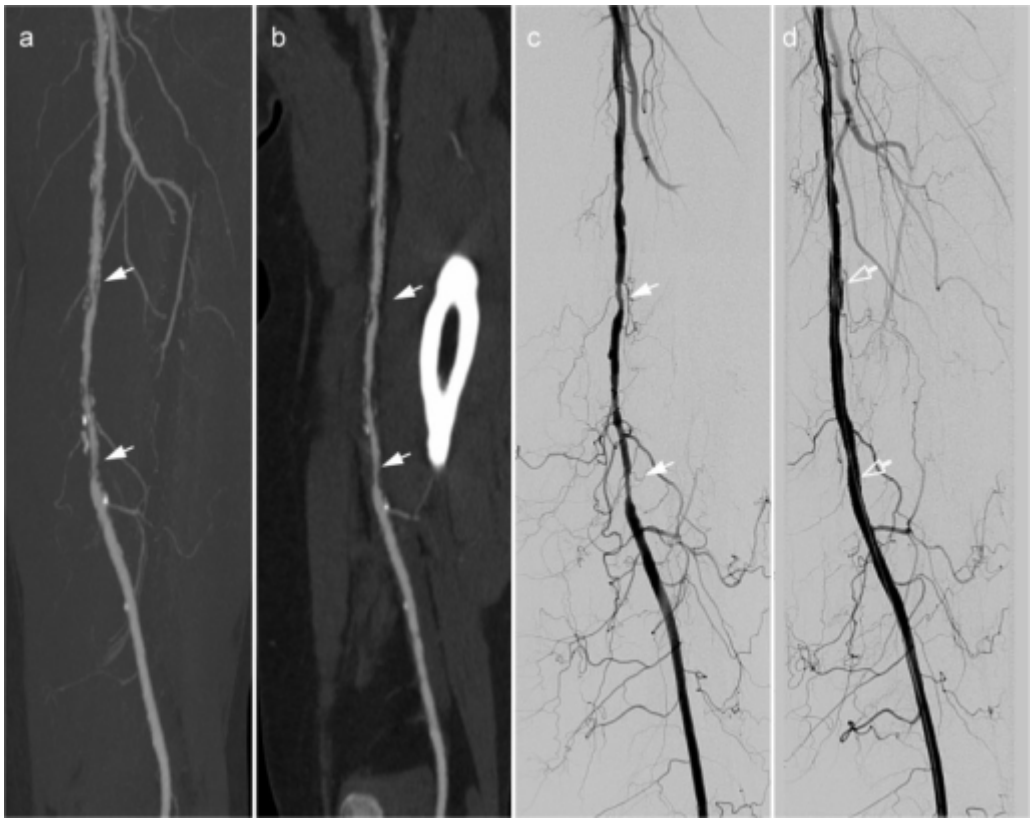

Image: “Example of a run-off CTA with sufficient diagnostic confidence and diagnostic image quality.69 y old female with intermittent claudication of the left lower leg (Fontaine stage IIB). Run-off CTA showed multiple stenoses (white arrows) of the left superficial femoral artery (TASC B) in the MIP images (a) and curved MPR (b). Stenoses were comfirmed by DSA (c) and successfully treated by percutaneous transluminal angioplasty and stenting (d, empty white arrow).” by Werncke, T., et al. License: CC BY 4.0

Differential Diagnoses

Vascular Diseases Similar to Atherosclerosis

In addition to atherosclerosis, there are other vascular diseases that cause structural wall changes and that can lead to stenosis. Examples include inflammatory diseases that cause 5% of stenotic vascular diseases. Inflammation may be caused by autoimmune or infectious processes, wherein the former clearly prevails.

If there is inflammation, the vascular wall thickens due to inflammatory infiltrates and secondary vessel wall edema. If the endothelium is damaged, thrombosis may be formed. Excluding stenosis, the inflammatory process can lead to vascular wall dilation or dissection.

Autoimmune Diseases Similar to Atherosclerosis

Among autoimmune diseases, **Buerger’s Disease** (**thromboangiitis obliterans**), **giant cell arteritis,** or **Takayasu arteritis** can be possible causes of vessel wall inflammation.

Bacteria such as *E. coli, S. aureus,* and herpes virus can also cause vessel wall inflammation.

Mechanical Damage

Mechanical damage, such as trauma to arterial vessels, can also cause stenosis, often by secondary inflammatory changes. Malignant tumors can cause infiltrative growth in the vascular wall. Even benign tumors can result in vasoconstriction by external compression.

Treatment

Treatment of atherosclerosis includes lifestyle modifications, medications, and surgical intervention.

Note:

Smoking cessation, healthy diet, adequate physical activity, and control of underlying diseases such as diabetes mellitus and hypertension lower the risk of atherosclerosis.

Non-pharmacological Treatment (lifestyle modifications)

These include weight normalization in combination with sufficient aerobic physical activity such as jogging, swimming, or cycling and eating a healthy diet. Smoking cessation is also important, as well as avoiding stress.

Walking Exercise Strategy

Exercising, such as walking regularly at least 30 continuous minutes 3 times per week can improve symptoms by encouraging the formation of new, collateral blood vessels and improving muscle efficiency. Many patients experience a dramatic increase in the distance they are able to walk without pain. Patients can also benefit from a vascular rehabilitation program, involving 45 minutes of supervised exercise weekly.

Pharmacological Treatment

Pharmacological treatment aims to control the modifiable risk factors of atherosclerosis. Antihypertensives, lipid-lowering agents, and anticoagulation medications are examples of what we might use in the treatment of atherosclerosis.

Complications

Complications include IHD and **angina pectoris, cerebrovascular** insufficiency, PAD, and renal artery stenosis. **Subclavian steal syndrome** or **mesenteric stenosis** can also result from chronic stenosis.

Acute vascular occlusions can also cause complications. Mesenteric infarction, renal or splenic infarction, as well as a transient ischemic attack (TIA) and stroke, are among the acute complications. Aneurysms at various vessel segments, such as **infrarenal** or **thoracic aortic aneurysms (with possibly thoracic aortic dissection),** as well as an **iliac** or **popliteal aneurysms,** are potential consequences of atherosclerosis.

Prevention

Reduction of modifiable risk factors is important. Prevention is aimed primarily at promoting a healthy diet, adequate physical activity in the form of aerobic exercise, and

controlling underlying diseases such as diabetes mellitus and hypertension. Smoking cessation is the most important preventive measure against atherosclerosis and its complications.

Dyslipidemia

Definition

Dyslipidemia is a disorder of lipid metabolism that is clinically defined as the presence of one of the following abnormalities: elevated plasma triglycerides (TG), elevated total cholesterol (TC), high levels of low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL). The specific population values will differ according to age, gender, and race. It is one of the main causes for the development of atherosclerosis.

Etiology

Causes of dyslipidemia can be primary as in familial hypercholesterolemia or secondary to underlying diseases such as diabetes mellitus, hypothyroidism, nephrotic syndrome, and hepatic diseases.

Clinical Features

Dyslipidemia is usually asymptomatic. A dyslipidemia is present in >70% of patients with premature coronary heart disease. Yellowish fatty accumulations (xanthomas) are sometimes present around patients' eyes and over the joints or tendons. Other clinical features of dyslipidemia include corneal arcus ("arcus senilis"), and hepatosplenomegaly. Most often, dyslipidemia is diagnosed on routine investigations or after a cardiovascular event, e.g., myocardial infarction or stroke. The most important dyslipidemia to know is familial hypercholesterolemia (FH) because it is one of the most common serious hereditary disorders, with heterozygotes occurring in 1/250 people. FH has an autosomal dominant pattern of inheritance and is caused by mutations in the genes encoding the LDL receptor (85% cases), ApoB protein (5–10% cases), or activating mutations of PCSK9 (1–2% cases). Hypercholesterolemia develops as a consequence of impaired transport of LDL into the cells. Homozygotes have a greater increase in serum cholesterol and a higher frequency of ischemic heart disease.

Frederickson Classification of Lipid Disorders

Type	Typical Lipid Levels	Lipoprotein Abnormality
I	TG > 99th %tile;	Chylomicrons
IIa	TC > 90th %tile; apoB ≥ 90th %tile (depends on type)	LDL
IIb	Depending on type, TC and/or TG ≥ %tile and apo B ≥ 90th%tile	LDL and VLDL
III	TC and TG > 90th %tile	Remnants of VLDL (Intermediate density lipoprotein) and chylomicrons
IV	TC > 90th %tile; depending on type, +/- TG > 90th %tile, or low HDL	VLDL
V	TG > 99th %tile	VLDL and chylomicrons

TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; HDL: high-density lipoprotein

Treatment

Non-Pharmacological Treatment (Lifestyle Modification)

Lifestyle modifications remain one of the most important therapeutic option for the

control of dyslipidemia. These modifications include:

- Dietary changes: reduce saturated fats and cholesterol intake.
- Weight reduction if overweight.
- Daily aerobic exercise or regular exercise.

High-yield fact:

Regular exercise is proven to increase HDL and decrease LDL levels.

Pharmacological Treatment

1. **Statins**

A moderate-intensity statin is recommended by the American Heart Association for primary prevention of ASCVD in: adults 40–75 years of age without diabetes mellitus, with LDL-C levels ≥70 mg/dL, and a 10–year atherosclerotic cardiovascular disease risk of 7.5–20%.

High-intensity statin therapy is recommended for high-risk patients (10–year risk of ASCVD > 20%) or those who already have ASCVD.

Note 1:

- The goal is to achieve a 50% reduction of the baseline LDL value.

Note 2:

- High-intensity statins include rosuvastatin 20 or 40 mg and atorvastatin 40 or 80 mg.
- Moderate-intensity statins include rosuvastatin 5 or 10 mg and atorvastatin 10 or 20 mg.

Contraindications to Statins

Statins are contraindicated in patients with active liver disease and in pregnancy. The main side effects of statins are:

- Myopathies (1%)
- Rhabdomyolysis (0.2%)
- Elevated liver function tests (2%)

Other side effects of statins include confusion, forgetfulness, dementia, depression, and erectile dysfunction.

Introduction of statins in the management of hyperlipidemia has improved the prognosis of IHD.

Statins were also found to be effective in lowering the risk of recurrent stroke in patients with a previous history of cerebrovascular disease. Although a definite mortality benefit has been more difficult to consistently demonstrate with statin treatment, intense LDL-C lowering lowers the risk of all-cause death in those at very high risk. Initiating statins to lower LDL cholesterol levels in the acute setting of a cerebrovascular accident was proven to be effective in improving the clinical outcome and lowering the disability of such patients.

2. **Non-statin Therapy**

Ezetimibe inhibits absorption of cholesterol at the brush border of the small intestine via

the sterol transporter, Niemann-Pick C1-Like1 (NPC1L1), and is offered to patients who cannot tolerate statins. PCSK9 monoclonal antibodies (alirocumab and evolocumab) bind free plasma PCSK9, which is an enzyme that degrades the receptor for LDL (LDL-R), leading to higher hepatic LDL-R expression and lower plasma LDL-C levels. This treatment is recommended for those whose LDL-C remains above 70 mg/dL.

Other lipid-lowering medications that can be used to lower the LDL cholesterol level include icosapent ethyl (an omega-3 fatty acid) and fibrates (more often used for hypertriglyceridemia). Bile acid sequestrants (e.g., cholestyramine, colestipol, and colesevalam) and nicotinic acid (niacin) are rarely used because of their side effects; however, nicotinic acid is used to lower lipoprotein(a).

Review Questions

1. **Which vessel or segment is most likely affected by atherosclerosis?**
    A. Arteries in the extremities
    B. All coronary arteries
    C. Intracranial arteries
    D. Carotid artery bifurcation
    E. Renal arteries
2. **What best describes the composition of atherosclerotic plaque?**
    A. Lipids
    B. Lipids and cellular debris
    C. Smooth muscle
    D. Fibrin
    E. Collagen
3. **Which of the following is most likely not a secondary disease of atherosclerosis?**
    A. Peripheral artery disease
    B. Coronary heart disease
    C. Prinzmetal angina
    D. Stroke link
    E. Mesenteric artery stenosis

Answers: 1D, 2B, 3C

References

Davies, M. J. (1993). *Atherosclerosis*. London Etc: BMJ Publishing Group.

Gotto, A. M., & Upjohn Company. (1992). *Atherosclerosis.* Kalamazoo, MI: Upjohn.

Harrison, M. (2017). *Cardiovascular system.* Oxford Medicine Online. doi:10.1093/med/9780198765875.003.0039

S., R. (2004). Chapter 1. Approach to Cardiovascular Diseases. In *Clinical Diagnosis Cardiovascular System, 1-5.* doi:10.5005/jp/books/10125_1.

Stanner, S. (2008). *Cardiovascular Disease.* Oxford: John Wiley & Sons.

Notes