Atherosclerosis (Atherosclerotic Cardiovascular Disease) — Definition and Pathology

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Atherosclerosis is an incurable disease, but for which there are clearly defined risk factors that often can be reduced through a change in lifestyle and behavior of the patient. It is the most abundant primary disease of the arterial vascular system and is responsible for coronary heart disease, the leading cause of death worldwide.

Definition of Atherosclerosis

The term atherosclerosis is derived from the words “atheroma” (focal plaques) and “sclerosis” (multiplication of connective tissue). The changes of 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 vessel lumen.

Atherosclerosis includes atherosclerosis, media sclerosis, and arteriolsclerosis.
Epidemiology of Atherosclerosis

Atherosclerosis is the leading cause of death in industrialized countries. Cardiovascular disease kills more people each year than Alzheimer’s, accidents, and cancer combined. Over 152,000 Americans killed by CVD each year are under the age of 65. In 2002, 32% of deaths from CVD occurred prematurely (i.e., before age 75, which is close to the average life expectancy).

Etiology of Atherosclerosis

Atherosclerosis is an inflammatory disease of the vessels, which is due to a reaction to oxidized LDL-cholesterol. Storage of lipids, calcium and cellular debris occurs mostly in the intima of large and medium-sized arteries. This leads to a thickening of the vessel walls and the formation of plaques.
Risk factors are defined as modifiable and non-modifiable factors. Non-modifiable risk factors are male gender, age and family history. The modifiable risk factors can be further divided into first and second order risk factors.

**First order modifiable**

- **Nicotine abuse**: Smoking promotes an early emergence and rapid progression of atherosclerosis.
- **Arterial hypertension**: Through increased pressure loads, damage occurs faster in the **endothelium**. Hypertension is a major risk factor for the development of cerebrovascular insufficiency.
- **Diabetes mellitus**: Increased phagocytosis and endothelial damage are the results of reactive glycosylation due to increased blood glucose levels.
- **Hyperlipoproteinemia**: Excessive LDL cholesterol increases the risk of atherosclerosis, especially when combined with low HDL cholesterol levels.

**Second order**

Second order risk factors include lack of exercise, stress, android obesity, **hyperuricemia**, **triglyceridemia**, **fibrinogenemia**, **homocysteinemia**, **glucose tolerance disorders**, **chronic renal failure**, and increased **lipoprotein (a)**.

**Classification of Atherosclerosis**

A classification can be made depending on the affected vessels. We distinguish between microangiopathies affecting the large and medium-sized arteries, and microangiopathy that occurs in the arterioles, capillaries or venules and is usually found in diabetes mellitus.
• 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

Symptoms and Clinical Diagnosis of Atherosclerosis

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

Diagnosis of Atherosclerosis

History and physical examination of atherosclerosis

The history is taken to identify risk factors, such as family history. Co-morbidities and the use of medication and walking distances should also be asked.

Physical examination can already provide information about the skin color and temperature or evidence of existing ulcerations of circulatory disorders. The heart should also be auscultated.

EKG or stress EKG can also 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, should 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 done. Other tests include:

- Complete blood count
- Sodium and potassium
 Diagnostic Imaging

Sonography

Ultrasonography can be used to assess superficial vessels and detect morphological changes. The thickness of the vessel walls can also be determined this way. Doppler sonography offers a good, non-invasive way to take a better look at the vessels. It is used for both the closure and perfusion measurement and the determination of the ankle-brachial index, as well as to measure the flow velocity pulses.

The (color) duplex sonography combines the two methods, and allows the examination of morphologically conspicuous vessel sections and gives a color code, depending on the flow direction of the blood. The intravascular ultrasound (IVUS) can be used to assess the coronary arteries.

An echocardiogram can be done to assess cardiac function (cardiac structure, ejection fraction, contractility)

Angiography

CT and MR angiography also offer the advantage of non-invasive diagnostics over conventional angiography. The presentation is detailed and enables 3D reconstruction for precise treatment planning. The 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 the stent angioplasty, and is still the gold standard in terms of accuracy of vascular imaging.
Pathology of Atherosclerosis

Initially, there a deposit of LDL cholesterol in the intima of the vessel walls occurs. This is oxidized, and it is followed by a local inflammatory response, so monocytes migrate into the tissue. If they phagocytize the LDL cholesterol, foam cells with embedded lipid droplets are created. 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), or at the carotid bifurcation).

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 confirmed by DSA (c) and successfully treated by percutaneous transluminal angioplasty and stenting (d, empty white arrow).” by Openi. License: CC BY 4.0

In the course, an increased amount of LDL cholesterol is deposited and macrophages appear and release fat. This causes an accumulation of lipids and cellular debris in the intima. Different cells of the vessel walls release mediators, so that muscle cells from the tunica media migrate into the intima.

The fatty core is surrounded by connective tissue and is not accessible from the outside so that the stored LDL cholesterol cannot be degraded. These plaques may contain newly formed vessels that originate from the vasa vasorum and can cause bleeding into the plaque.

In the growing plaques, calcium is also accumulated. Tears in the endothelium activate the coagulation cascade, causing thrombosis. The plaques initially develop extraluminally. If more than 40 % of the lumen is obstructed, stenosis of the vessel occurs. Due to damage of the vascular wall, NO synthesis is also disrupted, which causes endothelial dysfunction.

Plaques that have a large fatty core and only a thin fibrous cap are at risk to rupture. The coagulation system is so strongly activated under certain circumstances that it can lead
to a complete thrombotic occlusion of a vessel. 90% of the closures in a myocardial infarction are due to this.

The release of cholesterol due to a plaque rupture can cause cholesterol embolisms by spreading to remote vessels, such as in kidney.

Another consequence of atherosclerosis is the formation of aneurysms on the basis of changed atherosclerotic vascular tissue. Due to prolonged restructuring processes, the supply of the tunica media may be damaged, so that the tissue atrophies and the stability of the vessel walls decreases.

Whether endothelial dysfunction (“Response-to-Injury Hypothesis”) or the oxidation of LDL cholesterol (“lipoprotein induced-atherosclerosis hypothesis”) is ultimately the starting point of plaque formation is still unclear and controversial.

### Differential Diagnoses

#### Vascular diseases similar to atherosclerosis

In addition to atherosclerosis, there are other vascular diseases that cause structural wall changes and thus, lead to stenosis. Examples include inflammatory diseases, which however cause only 5% of stenotic vascular diseases. Cause of the inflammatory processes may be autoimmune or infectious processes, wherein the autoimmune clearly prevail.

If there is an inflammation, the vascular wall thickens due to inflammatory infiltrates and secondary vessel wall edema. If the endothelium is damaged, thrombosis may form here. Within the framework of a destroyed tunica media, not only stenosis but also dilations or dissections can be consequences of the inflammation.

#### Autoimmune diseases similar to atherosclerosis

Considering autoimmune diseases, Buerger’s Disease (thromboangiitis obliterans) and giant cell arteritis or Takayasu arteritis can be a possible cause of inflammation in the vessel walls. Infectious inflammations cause bacteria such as E. coli and S. aureus, or herpes viruses.

#### Mechanical damage

Mechanical damage to arterial vessels can also cause stenosis. This can be caused by trauma or surrounding tissue. Even benign tumors can have vasoconstrictive results. In malignant tumors, the vascular wall can also be affected by infiltrative growth.

### Treatment of Atherosclerosis

Include lifestyle changes, pharmacological, and surgical. All are aimed at reduction of risk factors.

#### Non-pharmacological treatment in atherosclerosis

Include weight normalization in combination with sufficient exercises, such as jogging, swimming or cycling, and a healthy, fat-modified diet. Smoking cessation is also important, as well as avoiding stress.
Walking exercise:

- Exercise such as walking regularly
- At least 30 continuous minutes three 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 weekly 45 minutes of supervised exercise

Drug therapy

Is aimed at treating hypertension, diabetes mellitus, hypertriglyceridemia, and dyslipoproteinemias. Thromboembolism prophylaxis is also indicated.

Complications

Include coronary artery disease and angina pectoris, cerebrovascular insufficiency, PAD, and renal artery stenosis. Subclavian steal syndrome or mesenteric stenosis can also result from the chronic stenosis.

Acute vascular occlusions can also cause complications. Mesenteric infarct, 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 an infrarenal or thoracic aortic aneurysm or thoracic aortic dissection as well as iliac or popliteal aneurysms are consequences of atherosclerosis.

Prevention of Atherosclerosis

Reducing risk factors to prevent atherosclerosis

Reduction or prevention of modifiable risk factors is important. Prevention is aimed primarily at a healthy diet, adequate physical activity in the form of aerobic exercise and controlling underlying diseases such as diabetes mellitus and hypertension.

But the most important factor is smoking cessation!

Review Questions

The correct answers can be found below the references.

1. Which vessel segments are most likely affected by atherosclerosis?
   - A. Peripheral vascular sections
   - B. All heart disease vessels
   - C. Intracranial vessels
   - D. Carotid bifurcation
   - E. Vessels of the extremities

2. What does plaque most likely consist of?
   - A. Lipids
   - B. Lipids and cellular debris
C. Calcium
D. Blood
E. Air

3. What’s most likely not a secondary disease of atherosclerosis?
   
   A. PAD
   B. Coronary heart disease
   C. Prinzmetal angina
   D. Apoplexy
   E. Mesenterial stenosis

References


Correct answers: 1D, 2B, 3C

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