International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Atherosclerosis: An Updated Review of Pathophysiology and Treatment Strategies

Tanuja Ashok Shete[1], Sandhya Vijay Patil[2], Dhanashri Yogesh Shelar[3]

[1]Research Scholar, Indrayani Vidya Mandir's Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune-412101
Email: *tanujashete5[at]gmail.com*

[2]Assistant Professor, Indrayani Vidya Mandir's Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune-412101
Email: *sandhyapatil.kbiper[at]gmail.com*

[3]Research Scholar, Indrayani's Vidya Mandir Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune-412101
Email: *dhanashrishelar1012[at]gmail.com*

Abstract: ***Atherosclerosis is a chronic, progressive vascular disease characterized by lipid accumulation, inflammation, and fibrous plaque formation within the arterial intima. It remains one of the leading causes of morbidity and mortality worldwide, contributing significantly to coronary artery disease, stroke, and peripheral arterial disease. The disease is initiated by hyperlipidemia, endothelial dysfunction, and the oxidation of low-density lipoproteins, which trigger inflammatory responses and the formation of atherosclerotic plaques. Progressive plaque growth, vascular remodeling, calcification, and thrombosis ultimately impair blood flow and increase the risk of life-threatening cardiovascular events. This review summarizes the current understanding of the pathophysiology of atherosclerosis, highlighting the sequential stages of lesion development, genetic and environmental risk factors, and recent advances in disease mechanisms. It also discusses current preventive strategies, including lifestyle modification and risk-factor management, alongside established and emerging therapeutic approaches such as lipid-lowering agents, antihypertensive therapy, antithrombotic medications, and revascularization procedures. By integrating recent scientific and clinical evidence, this review provides an updated perspective on the mechanisms, prevention, and treatment of atherosclerosis, with an emphasis on improving cardiovascular outcomes and identifying future directions for research and clinical practice.***

Keywords: Atherosclerosis, Hyperlipidemia, CVS diseases, Atheroma

1. Introduction

Atherosclerosis is the result of hyperlipidemia and lipid oxidation and has always been a major cause of mortality in developed countries. It is a disease of vascular intima, in which all the vascular system from aorta to coronary arteries can be involved and is characterized by intimal plaques. Currently, atherosclerosis is a common disease in which fatty deposits called atheromatous plaques appear in the inner layers of arteries. Formation of these plaques starts with the deposition of small cholesterol crystals in the intima and its underlying smooth muscle. Then the plaques grow with the proliferation of fibrous tissues and the surrounding smooth muscle and bulge inside the arteries and consequently reduce the blood flow. Connective tissue production by fibroblasts and deposition of calcium in the lesion cause sclerosis or hardening of the arteries. Finally, the uneven surface of the arteries results in clot formation and thrombosis, which leads to the sudden obstruction of blood flow. This review provides an overview of the disease with an emphasis on recent developments. We first discuss the growth of atherosclerotic lesions, from initiation to advanced lesions and aging. This is followed by a discussion of genetic approaches and the major genetic and environmental risk factors for the disease. We conclude with a discussion of clinical aspects and future directions. Due to limitations in the length of the review, we largely refer to recent reviews rather than original articles except for recent major events. Prevention guidelines include eating a healthy diet, exercising, not smoking, and maintaining a normal body weight. Treatment of established atherosclerotic disease may include medications to lower cholesterol such as statins, blood pressure medication, and anticoagulant therapies to reduce the risk of blood clot formation. As the disease state progresses, more invasive strategies are applied, such as percutaneous coronary intervention, coronary artery bypass graft, or carotid endarterectomy. In some individuals, genetic factors are also implicated in the disease process and cause a strongly increased predisposition to development of atherosclerosis.

2. Signs and Symptoms

Atherosclerosis is typically asymptomatic for decades because the arteries enlarge at all plaque locations; thus, there is no effect on blood flow. Even most plaque ruptures do not produce symptoms until enough narrowing or closure of an artery, due to clots, occurs. Signs and symptoms only happen after severe narrowing or closure impedes blood flow to different organs enough to induce symptoms. Most of the time, patients realize that they have the disease only when they experience other cardiovascular disorders such as stroke or heart attack. These symptoms, however, still vary depending on which artery or organ is affected. Early atherosclerotic processes likely begin in childhood. Fibrous and gelatinous lesions have been observed in the coronary arteries of children. Fatty streaks have been observed in the coronary arteries of juveniles. While coronary artery disease is more prevalent in men than women, atherosclerosis of the cerebral arteries and strokes equally affect both sexes.

Marked narrowing in the coronary arteries, which are responsible for bringing oxygenated blood to the heart, can produce symptoms such as chest pain of angina and shortness of breath, sweating, nausea, dizziness or light headedness, breathlessness or palpitations. Abnormal heart rhythms called arrhythmias—the heart beating either too slowly or too quickly—are another consequence of ischemia. Carotid arteries supply blood to the brain and neck. Marked narrowing of the carotid arteries can present with symptoms such as a feeling of weakness; being unable to think straight; difficulty speaking; dizziness; difficulty in walking or standing up straight; blurred vision; numbness of the face, arms, and legs; severe headache; and loss of consciousness. These symptoms are also related to stroke (death of brain cells). Stroke is caused by marked narrowing or blockage of arteries going to the brain; lack of adequate blood supply leads to the death of the cells of the affected tissue. Peripheral arteries, which supply blood to the legs, arms, and pelvis, also experience marked narrowing due to plaque rupture and clots. Symptoms of the narrowing are pain and numbness in the arms or legs. Another significant location for plaque formation is the renal arteries, which supply blood to the kidneys. Plaque occurrence and accumulation lead to decreased kidney blood flow and chronic kidney disease, which, like in all other areas, is typically asymptomatic until late stages.

In 2004, US data indicated that in ~66% of men and ~47% of women, the first symptom of atherosclerotic cardiovascular disease was a heart attack or sudden cardiac death (defined as death within one hour of onset of the symptom). Case studies have included autopsies of U.S. soldiers killed in World War II and the Korean War. A much-cited report involved the autopsies of 300 U.S. soldiers killed in Korea. Although the average age of the men was 22.1 years, 77.3 percent had "gross evidence of coronary arteriosclerosis.

3. Risk factors

The atherosclerotic process is not well understood. Atherosclerosis is associated with inflammatory processes in the endothelial cells of the vessel wall associated with retained low-density lipoprotein (LDL) particles.[28][29] This retention may be a cause, an effect, or both of the underlying inflammatory process.

The presence of the plaque induces the muscle cells of the blood vessel to stretch, compensating for the additional bulk. The endothelial lining then thickens, increasing the separation between the plaque and the lumen. The thickening somewhat offsets the narrowing caused by the plaque's growth. Moreover, it causes the wall to stiffen and become less compliant to stretching with each heartbeat.

Modifiable
- Western pattern diet
- Abdominal obesity
- Diabetes
- Dyslipidemia
- High blood cholesterol
- High blood pressure
- Elevated concentrations of apolipoprotein B (ApoB)-containing lipoproteins (such as LDL particles), for which LDL-cholesterol (LDL-C) is the most commonly used surrogate marker High saturated fat diet Trans fat
- Tobacco smoking
- Bacterial infections
- HIV/AIDS
- Psychological stress
- Sedentary lifestyle

Nonmodifiable
- Biological sex
- South Asian descent
- Advanced age
- Genetic abnormalities
- Family history
- Coronary anatomy and branch pattern

Lesser or uncertain
- Thrombophilia
- Elevated triglycerides
- Systemic inflammation
- Hyperinsulinemia
- Sleep deprivation
- Air pollution
- Arsenic poisoning
- Hypothyroidism
- Periodontal disease

Dietary

The relation between dietary fat and atherosclerosis is controversial. The USDA, in its food pyramid, promotes a diet of about 64% carbohydrates from total calories. The American Heart Association, the American Diabetes Association, and the National Cholesterol Education Program make similar recommendations. In contrast, Prof Walter Willett (Harvard School of Public Health, PI of the second Nurses' Health Study) recommends much higher levels of fat, especially of monounsaturated and polyunsaturated fat. These dietary recommendations reach a consensus, though, against consumption of trans fats.

The role of eating oxidized fats (rancid fats) in humans is not clear. Rabbits fed rancid fats develop atherosclerosis faster. Rats fed DHA-containing oils experienced marked disruptions to their antioxidant systems, and accumulated significant amounts of phospholipid hydroperoxide in their blood, livers and kidneys.

Rancid fats and oils taste very unpleasant in even small amounts, so people avoid eating them.[58] Measuring or estimating the actual human consumption of these substances is challenging. Highly unsaturated omega-3 rich oils such as fish oil, when being sold in pill form, can hide the taste of oxidized or rancid fat that might be present. In the US, the health food industry's dietary supplements are self-regulated and outside of FDA regulations. To protect unsaturated fats from oxidation, it is best to keep them cool and in oxygen-free environments

Pathophysiology

Atherogenesis is the developmental process of atheromatous plaques. It is characterized by arterial remodeling, leading to the subendothelial accumulation of fatty substances called

plaques. The buildup of an atheromatous plaque is a slow process, developed over several years through a complex series of cellular events occurring within the arterial wall and in response to several local vascular circulating factors. One recent hypothesis suggests that, for unknown reasons, leukocytes, such as monocytes or basophils, begin to attack the endothelium of the artery lumen in cardiac muscle. The ensuing inflammation leads to the formation of atheromatous plaques in the arterial tunica intima, a region of the vessel wall located between the endothelium and the tunica media.

Chronic inflammation within the arterial wall, driven by immune cells (e.g., macrophages), accelerates atherosclerotic plaque instability by promoting collagen breakdown and thinning the fibrous cap, increasing the likelihood of rupture and thrombosis. The bulk of these lesions is made of excess fat, collagen, and elastin. At first, as the plaques grow, only wall thickening occurs without narrowing. Stenosis is a late event, which may never happen and is often the result of repeated plaque rupture and healing responses, not just the atherosclerotic process. Autopsy studies have shown that the prevalence of coronary artery atherosclerosis in males from the United States, with an average age of 22.1 years, who died in war, ranges from 45% to 77.3%

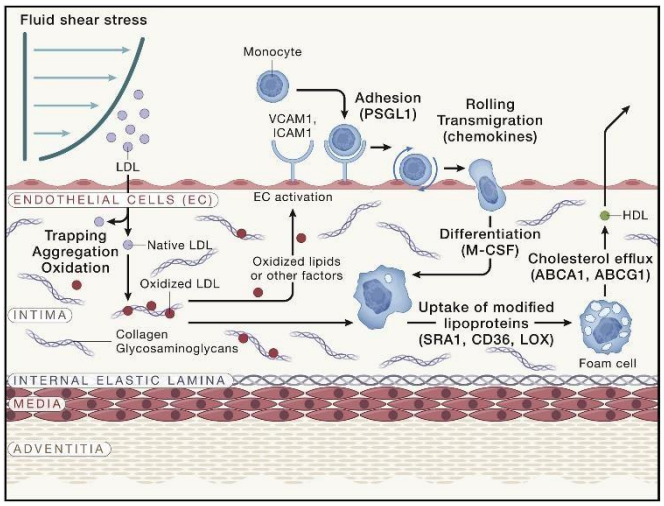

Figure 1: Occurrence of Atheroma

Cholesterol is delivered into the vessel wall by cholesterol containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process. The process is worsened if there is insufficient high-density lipoprotein (HDL), the lipoprotein particle that removes cholesterol from tissues and carries it back to the liver.

Atheroma formation

Severe damage to vascular tissue happens when adjacent SMC and endothelial cells secret small peptides such as cytokines and growth factors such as interleukin 1 (IL-1), and TNF (which causes cell growth). These factors cause SMC to migrate into the luminal side of vessel wall. In this condition, smooth muscle cell migration and synthesized extracellular matrix form the fibrous cap. Fibrous cap is composed of collagen-rich fiber tissues, SMC, macrophages and T lymphocytes. All of them form the mature atherosclerosis plaque and bulge into the channel and reduce the blood stream in the vessels. Macrophages and T lymphocytes are found in the borders of developed plaque. Macrophages secrete meta proteinase, which contribute to the lysis of extracellular matrix. T cells produce TNF-α which prevents the collagen synthesis in the SMC. These processes weaken the formed plaque shaped fibrous cap and can destroy it. Destruction of fibrous cap exposes collagen and lipids to blood stream which contributes to accumulation and adhesion of platelets and blood clot formation which may suddenly block the blood stream.

Atherosclerotic plaque formation

Atherosclerotic plaques constituents are as follows:

- Vascular epithelium: Vascular epithelium reacts with macromolecules and blood components to increase the protein transfer in plasma.
- Arterial smooth muscle: The maintenance of vascular repair and metabolism of blood products including lipids, and the secretion of various cytokines, is essential in the control of vascular wall tonus
- Lymphocytes: They may participate in the immune reactions. The core of plaque is composed of cell lesions, foam cells, calcium, cholesterol esters, and a mass of fatty substances. Lipid nucleus is a pale yellow mass, which its color is caused by carotenoid pigments.

References

[1] Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592(7855):524–533.
[2] Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. *Nat Rev Dis Primers*. 2019;5(1):56.
[3] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685–1695.
[4] Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114(12):1852–1866.
[5] Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47(8 Suppl):C7–C12.
[6] Lusis AJ. Atherosclerosis. *Nature*. 2000; 407(6801): 233–241.
[7] Gimbrone MA Jr, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res*. 2016;118(4):620–636.
[8] Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res*. 2016;118(4):535–546.
[9] Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2024 update: A report from the American Heart Association. *Circulation*. 2024; 149: e347–e913.
[10] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J*. 2020;41(1):111–188.
[11] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC Guideline on the management of blood cholesterol. *Circulation*. 2019; 139: e1082–e1143.

[12] Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020; 383: 1838–1847.
[13] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017; 377: 1119–1131.
[14] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017; 376: 1713–1722.
[15] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018; 379: 2097–2107.
[16] Libby P, Loscalzo J, Ridker PM, et al. Inflammation, immunity, and infection in atherothrombosis. *J Am Coll Cardiol*. 2018;72(17):2071–2081.
[17] Wolf D, Ley K. Immunity and inflammation in atherosclerosis. *Circ Res*. 2019;124(2):315–327.
[18] Roy P, Orecchioni M, Ley K. How the immune system shapes atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2022;42(8):e168–e182.
[19] Björkegren JLM, Lusis AJ. Atherosclerosis: Recent developments. *Cell*. 2022;185(10):1630–1645.
[20] Libby P, Hansson GK. From focal lipid storage to systemic inflammatory disease: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74(12):1594– 1607.