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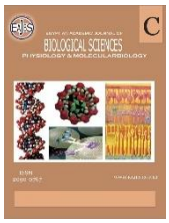

Atherosclerosis Review: Background, Ethology, Symptoms, Prevention and Control

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ABSTRACT

Atherosclerosis refers to the accumulation of lipids, cholesterol, and other substances on the inner and outer surfaces of the arteries, collectively known as plaque. This buildup can narrow arteries and reduce blood flow. If the plaque ruptures, a blood clot may form. While heart problems are the most common manifestation, atherosclerosis can affect arteries throughout the body. Atherosclerosis is a major cause of disease and mortality worldwide. This research emphasizes recent discoveries on atherosclerosis markers and risk factors while examining the processes and contributing factors of the disease. Treatment options for atherosclerosis include medical interventions and lifestyle modifications, such as quitting smoking, reducing cholesterol levels, managing blood sugar levels, exercising regularly, improving dietary habits, and controlling blood pressure. By adopting these measures, individuals can lower their risk of developing atherosclerosis and its complications. Regular monitoring and early intervention remain critical for effective management of this condition.

INTRODUCTION

Atherosclerosis is among the most prevalent cardiovascular disorders (CVDs), also known as coronary artery disease (CAD). This disease causes an accumulation of lipids, which leads to inflammation of the large arteries and, consequently, serious health problems such as stroke and myocardial infarction (MI). Clinically significant atherosclerosis, a disease that develops gradually and primarily affects the elderly, is the leading cause of mortality worldwide, even though its incidence is declining in certain nations (Mohd Nor *et al.*, 2019). Atherosclerotic lesions are characterized by the accumulation of lipids, smooth muscle cells, inflammatory cells, and debris over time. These compounds gather behind a layer of endothelial cells that coat the inner surface of blood vessels. Lesion growth commonly leads to a decrease of more than 50% in blood flow through the lumen, which can result in angina, particularly during physically demanding activities or stress. Lesions, especially those with an inflammatory and fatty composition, can become unstable and rupture.

This rupture can lead to a local clot in the coronary arteries, which may completely block blood flow and result in an MI. Additionally, there is a possibility that the blood clot could detach from the heart and travel to the brain, potentially causing a stroke *(Dichgans et al.*, 2019).

Atherosclerosis' molecular and cellular interaction mechanisms have been better understood recently. Atherosclerotic lesions that were previously unknown to have cellular heterogeneity have been discovered via single-cell RNA sequencing (scRNA-seq).

Furthermore, it has been recognized that aging-related mechanisms such as clonal hematopoiesis and senescence likely have a substantial impact. Moreover, there is an increasing body of research establishing a connection between the gut flora and atherosclerosis. The comprehension of the correlation between genetic and environmental risk factors for atherosclerosis and its association with cardiometabolic features is constantly evolving. Furthermore, notable progress has been made in the domains of therapy and diagnostics (Paul *et al.*, 2019).

Ethology:

ASCVD arises from a complex interplay of genetic, environmental, and lifestyle factors. The most prevalent risk factors include male gender, age (men and women above 45 and 55 years old, respectively), a strong family history (men and women younger than 55 and 56 years old, respectively), hypertension, diabetes mellitus, cigarette smoking, and hypercholesterolemia (LDL cholesterol) (Shafi *et al.*, 2019). Additionally, consuming diets high in trans and saturated fats, obesity, sedentary lifestyles, and specific genetic mutations increase the risk. While low levels of high-density lipoprotein (HDL) cholesterol are considered to increase the risk of atherosclerotic cardiovascular disease (ASCVD), the effectiveness of pharmaceutical therapies to raise HDL cholesterol levels in improving outcomes remains uncertain.
(Shafi *et al.*, 2019).

Epidemiology:

Atherosclerosis often lacks clear symptoms, complicating diagnosis. It is widely acknowledged as the primary underlying factor responsible for cardiovascular disease. Ischemic heart disease (IHD) and stroke are the main consequences of this condition, which primarily affects the heart and brain. IHD and stroke rank as the first and fifth leading causes of death worldwide, respectively (Ala-Korpela, 2019). An estimated 610,000 Americans die from heart disease annually in the United States, accounting for one out of every four deaths. With approximately 370,000 deaths each year, coronary heart disease is the leading cause of mortality in Western countries.

Additionally, an estimated 735,000 Americans experience a heart attack annually, comprising 210,000 recurrent attacks and 525,000 initial episodes. Reports indicate that 75% of acute myocardial infarctions result from plaque rupture. This occurrence is most prevalent in males aged 45 and older and increases in females aged 50 and older. (Watson *et al.*, 2019; Whelton *et al.*, 2019).

Among the top five causes of death in the United States, stroke is also the leading cause of long-term serious disability. Approximately 140,323 deaths annually in the U.S. are attributed to strokes, which affect about 795,000 people each year. Ischemic stroke, the most common type, is primarily caused by ASCVD. Numerous risk factors for atherosclerosis have been identified through epidemiologic research conducted in North America and Europe. Atherosclerosis, an inflammatory disease, may develop as a result of its impact on low-density lipoprotein (LDL) particles.(Carmona *et al.*, 2019).

Pathophysiology of Atherosclerosis:

Atherosclerosis initially manifests visually as a fatty streak, which consists of an aggregation of foam cells loaded with lipids within the intimal layer of an artery. The three primary components of atherosclerotic plaque, which develops from the fatty streak and is a hallmark of atherosclerosis, are inflammatory cells, fats, smooth muscle, calcium deposits, and thrombi embedded within the connective tissue matrix in varying states of organization. (Hartman *et al.*, 2021).

Atherosclerotic Plaque Formation:

Atherosclerosis is an inflammatory reaction to injury, regulated by specific cytokines throughout all stages, including initiation, progression, and the development of plaque complications such as myocardial infarction and stroke. Endothelial injury is believed to play a crucial role in initiating this

process. Nonlaminar or turbulent blood flow, such as at arterial branch sites, disrupts normal endothelial function and decreases the production of nitric oxide a potent vasodilator with anti-inflammatory properties. This turbulent flow also stimulates endothelial cells to produce adhesion molecules, which attract and bind inflammatory cells (Hartman *et al.,* 2021; Noonan *et al.,* 2022).

Risk factors for atherosclerosis, such as dyslipidemia, diabetes, cigarette smoking, and hypertension, as well as oxidative stressors like superoxide radicals, angiotensin II, systemic infections, and inflammation, all decrease nitric oxide production while promoting the release of adhesion molecules, proinflammatory cytokines, chemotactic proteins, and vasoconstrictors (Hartman *et al.,* 2021). The precise mechanisms behind these effects are not yet fully understood. Consequently, monocytes and T cells adhere to the endothelial surface, migrate beneath it, and establish a localized vascular inflammatory reaction. Within the subendothelium, monocytes differentiate into macrophages, Figure 1. Lipids, particularly LDL and VLDL cholesterol, bind to endothelial cells in the bloodstream and undergo oxidation in the subendothelium (Hartman *et al.*, 2021).

Fatty streaks, the early lesions of atherosclerosis, arise from the absorption of oxidized lipids and the transformation of macrophages into lipid-laden foam cells. A key source of lipids in plaques is ruptured vasa vasorum and intraplaque bleeding, which degrade erythrocyte membranes. Proinflammatory cytokines produced by macrophages attract and stimulate smooth muscle cell development, recruiting these cells to migrate from the media (Wang *et al.*, 2022). Dense extracellular matrix formation and smooth muscle cell proliferation are driven by several factors. The final product is a fibrous plaque located in the subendothelium, characterized by a fibrous cap composed of intimal smooth muscle cells surrounded by lipids (both intracellular and extracellular) and connective tissue. A process resembling bone formation leads to calcification within the plaque (Pierce & Feinberg, 2020).

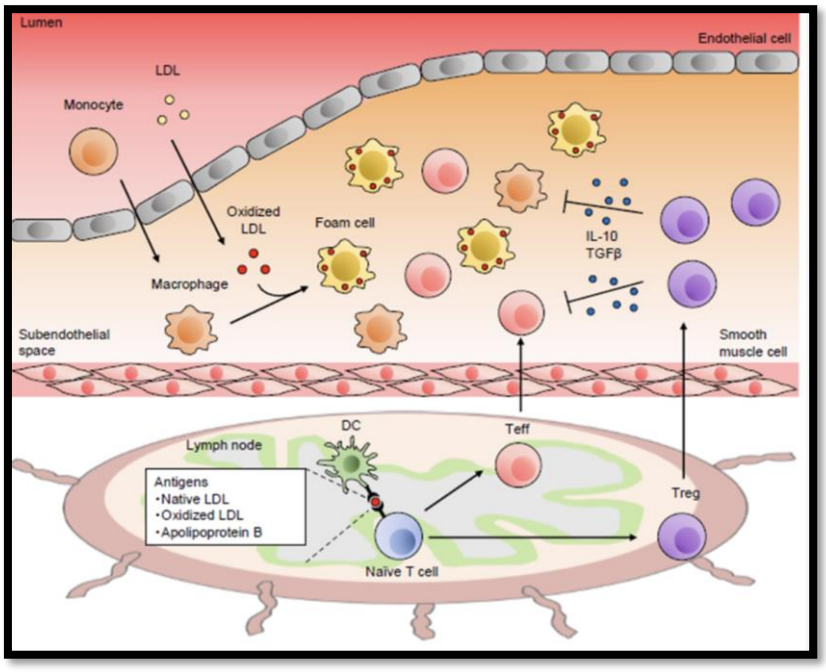

Fig. 1: illustrates the role of the immune system in atherosclerosis. Chronic vascular inflammation, driven by immune dysregulation, plays a critical role in the pathogenesis of atherosclerosis. Regulatory T cells (Tregs) protect against atherosclerosis by inhibiting the activation of various immune cells. Key elements involved include dendritic cells (DCs), interleukins (ILs), low-density lipoproteins (LDL), effector T cells (Teff), and transforming growth factor (TGF).

Plaque Stability and Rupture:

Both stable and unstable atherosclerotic plaques can occur. Stable plaques can regress, remain unchanged, or grow gradually over decades. These plaques may eventually narrow or completely block the artery. Unstable plaques, on the other hand, are more prone to spontaneous erosion, fissure, or rupture, which can lead to the sudden formation of blood clots, arterial blockage, and tissue death. Prior to causing stenosis that significantly impacts blood flow, unstable plaques are at risk of these disruptive events (McLeod et al., 2014; Tabas, 2010). Plaque stabilization can reduce illness and mortality rates, as shown in **Figure 2**. Unstable plaques, which are often not hemodynamically significant on angiography, are responsible for most clinical events. The balance between collagen deposition and degradation is a key determinant of the fibrous cap's strength and durability (Virmani *et al.,* 2005).

When a plaque ruptures and its contents are exposed to the bloodstream, macrophages contribute to thrombosis by carrying tissue factors that stimulate thrombin production in vivo. There are several possible outcomes: The plaque may undergo morphological changes and expand rapidly due to thrombus formation and incorporation (Sakakura *et al.,* 2013). Rapid thrombus occlusion of the arterial lumen can result in an acute ischemic episode. The thrombus may enlarge further.

Blood pooling within the plaque can cause swelling and immediate arterial obstruction. The plaque contents, rather than the thrombus, can dislodge and block downstream vessels (Pierce & Feinberg, 2020). Numerous factors influence plaque stability, including wall stress (cap fatigue), core size and location, plaque architecture in relation to blood flow, and the plaque's composition (fat, inflammation, smooth muscle, connective tissue, and thrombus percentage). Intraplaque bleeding, by promoting rapid growth and lipid deposition, may play a significant role in converting stable plaques into unstable ones (Bauriedel *et al.,* 1999).

Unstable coronary artery plaques are characterized by a thin fibrous cap, dense lipid core, and high macrophage content. These plaques often rupture irregularly, causing vessel lumen constriction of less than 50%. The composition of unstable carotid artery plaques is similar; however, they typically cause issues through profound stenosis, occlusion, or the accumulation of platelet thrombi, which embolize rather than rupture. Low-risk plaques, which are fewer in number and have thicker caps, can cause predictable exercise-induced stable angina and often limit the artery lumen by more than 50% (Virmani *et al.,* 2005).

Additionally, the clinical outcomes of coronary artery plaque rupture, including arrhythmias, are influenced by the anatomical position of the plaque, the balance of procoagulant and anticoagulant activity in the blood, and the myocardium's susceptibility (Bauriedel *et al.,* 1999).

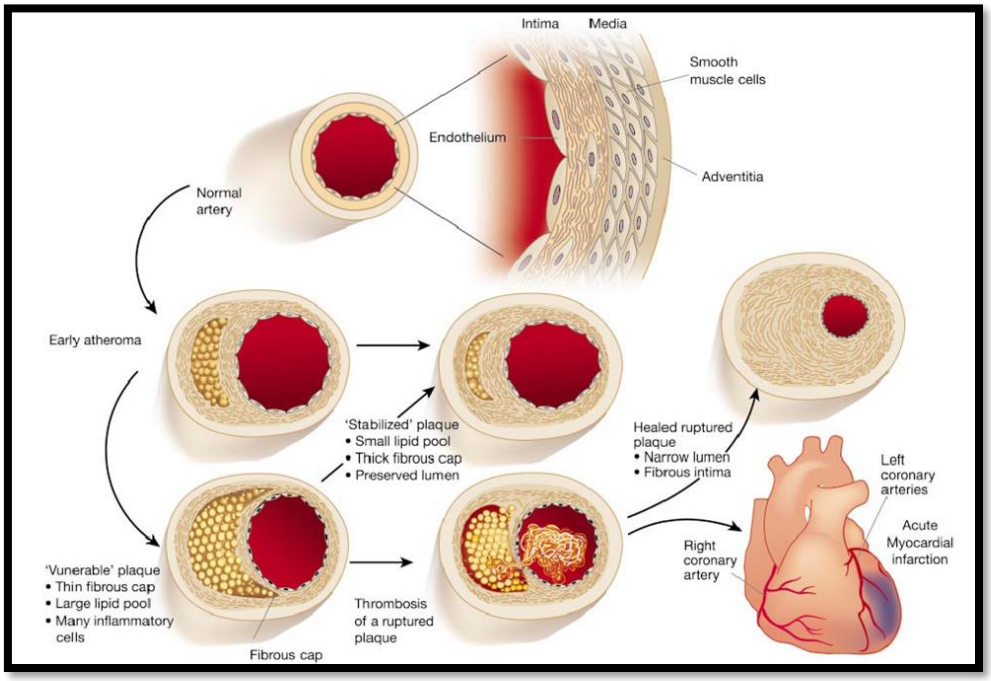

Fig. 2: Illustrates the evolution of atherosclerotic plaques.

Risk Factors for Atherosclerosis:

Metabolic Syndrome and Atherosclerosis:

Metabolic syndrome is a grouping of related elements, including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, and a prothrombotic and proinflammatory state, all of which are present in sedentary individuals with this condition. Although metabolic syndrome and insulin resistance are not the same, they may be closely related (Yusuf *et al.*, 2004).

By enhancing or intensifying endothelial dysfunction and inflammatory pathways in the vascular endothelium, dyslipidemia (high total, high LDL, or low HDL cholesterol), hypertension, and diabetes all contribute to atherosclerosis (White *et al.*, 2016). Dyslipidemia increases the uptake and oxidation of LDL in subendothelial cells. Oxidized lipids are antigenic, triggering a T cell-mediated immune response and causing inflammation of the artery wall. They also promote the synthesis of adhesion molecules and inflammatory cytokines (Collaboration, 2009).

While randomized trials and genetic studies suggest HDL plays a relatively minor role in atherogenesis, it was traditionally thought to protect against atherosclerosis by promoting reverse cholesterol transport and providing antioxidant enzymes to neutralize oxidized lipids. Hypertriglyceridemia may have a small independent role in atherogenesis, although its impact remains complex (Yusuf *et al.*, 2004).

The vascular inflammation caused by hypertension may involve pathways mediated by angiotensin II. Endothelial cells, vascular smooth muscle cells, and macrophages are targeted by angiotensin II to produce proatherogenic mediators, including proinflammatory cytokines, superoxide anions, growth factors, prothrombotic factors, and lectin-like oxidized LDL receptors (Thanassoulis *et al.*, 2013).

Advanced glycation end products produced in diabetes promote proinflammatory cytokine production by endothelial cells. Diabetes-induced oxidative stress and reactive oxygen radicals directly damage the endothelium, encouraging atherogenesis. In chronic renal disease, additional factors such as reduced apolipoprotein A-I levels, insulin resistance, elevated lipoprotein(a), homocysteine, fibrinogen, and C-reactive protein concentrations all contribute to

atherosclerosis development (Nordestgaard *et al.*, 2010).

Symptoms and Signs of Atherosclerosis:

Atherosclerosis can persist without symptoms for many years. Signs and symptoms arise when lesions block blood flow. Transient ischemic symptoms, such as stable exertional angina, transient ischemic episodes, and intermittent claudication, occur when persistent plaques narrow the arterial lumen by more than 70% (Wulsin & Singal, 2003). Lesions that do not initially impede blood flow may develop into severe or total stenosis due to vasoconstriction. Acute occlusion of a major artery caused by ruptured unstable plaques can result in symptoms such as myocardial infarction, unstable angina, ischemic stroke, or limb pain at rest. In some cases, atherosclerosis may result in sudden death, even in the absence of angina. Aneurysms and arterial dissection caused by atherosclerotic involvement of the artery wall can lead to discomfort, a pulsatile mass, absence of pulses, or death (Kim *et al.*, 2010).

Atherosclerosis Diagnosis:

A healthcare provider may look for aneurysms an abnormal bulging or expansion of an artery caused by weakening of the arterial wall slow wound healing, or a whooshing sound from a blocked artery, which are signs of weakened pulses. A cardiologist will assess heart sounds and recommend further testing if atherosclerosis is suspected. Tests may include blood tests to measure cholesterol levels, Doppler ultrasound to visualize arteries, and the ankle-brachial index to compare blood pressure in limbs and detect blockages (D. Arnett *et al.*, 2019). Advanced imaging, such as computed tomography angiography or magnetic resonance angiography, can create detailed images of major arteries. A cardiac angiogram involves a chest X-ray following the injection of radioactive dye into the heart arteries. Stress tests or exercise tolerance tests assess cardiac function, while an electrocardiogram (ECG or EKG) evaluates the heart's electrical activity (Hartman *et al.*, 2021).

Atherosclerosis Treatment and Management:

Addressing risk factors such as elevated LDL-C, blood pressure (BP), and diabetes is the most effective way to treat ASCVD. Patients should adopt a healthy diet rich in fiber, monounsaturated fats, fatty fish, fruits, and vegetables while avoiding saturated and trans fats (e.g., baked goods, red and processed meat, organ meats). Salt intake should be limited to less than 5 grams daily, and an exercise regimen of 90 to 150 minutes per week should be recommended.

Patients who smoke should be encouraged to quit and directed to cessation programs (Perez-Martinez et al., 2020). Statins are essential for reducing LDL cholesterol levels, thereby lowering the risk of cardiovascular events and mortality. Multiple medications may be necessary to control blood pressure, including diuretics, beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, and vasodilators (Spannella et al., 2019). Proper blood pressure management prevents strokes, with a target BP below 130/85 mmHg (Esper & Nordaby, 2019).

Managing diabetes involves dietary changes, physical activity, and therapies to maintain glycated hemoglobin (HbA1c) levels below 7%, BP below 130/85 mmHg, and LDL cholesterol below 100 mg/dL. For clinical ASCVD, revascularization procedures such as angioplasties and bypass surgeries may be recommended. Thrombolysis may also be used to treat CVA and acute limb ischemia caused by emboli or thrombi (D. K. Arnett *et al.*, 2019).

Declarations:

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