Understanding Atherosclerosis: Pathophysiologic Insights and Primary Prevention to Mitigate Coronary Events

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Abstract

Atherosclerosis represents the fundamental pathological process underlying ischemic heart disease, particularly acute coronary syndrome, and remains a major cause of cardiovascular morbidity and mortality worldwide. Its development is driven by a complex interplay of endothelial dysfunction, lipid deposition, inflammatory activation, and fibrous plaque formation, culminating in plaque rupture and subsequent coronary flow obstruction. In this paper, we comprehensively explore the pathophysiological mechanisms of atherosclerosis and discuss potential preventive strategies aimed at attenuating its progression and reducing the burden of ischemic heart disease.

Keywords: *Atherosclerosis, LDL, Inflammation, Acute Coronary Syndrome, Acute Myocardial Infarction*

INTRODUCTION

Atherosclerosis is a chronic arterial disease characterized by persistent vascular inflammation and the accumulation of lipid-laden plaques within the arterial wall. It represents the principal underlying cause of ischemic heart disease, including acute coronary, primarily through plaque rupture and subsequent thrombus formation that lead to partial or complete coronary artery occlusion [1]. Because atherosclerosis remains largely asymptomatic until its advanced stages, estimating its true epidemiological burden is challenging. Consequently, the epidemiology of cardiovascular diseases, particularly ischemic heart diseases, serves as a useful surrogate for assessing the population-level impact of atherosclerosis.

In the United States alone, approximately 735,000 myocardial infarctions and 610,000 cardiovascular-related deaths occur annually. Across Western countries, coronary heart disease continues to be the leading cause of mortality, accounting for nearly 370,000 deaths each year [1]. The South-East Asia Region (SEAR) encompasses more than 600 million people, the majority of whom are under 65 years of age [2]. Rapid population growth, persistent socioeconomic disparities, and accelerated globalization have collectively driven a marked epidemiological transition in the region. Over 80% of cardiovascular disease (CVD)–related deaths now occur in low- and middle-income countries, with Asia accounting for nearly half of the global cardiovascular disease burden [2].

Atherosclerosis, the key pathological mechanism of ischemic heart disease, develops through a multifactorial process initiated by endothelial dysfunction and lipid accumulation, progressing to plaque formation, destabilization, and rupture, ultimately resulting in vascular obstruction [3,4]. Intervening at critical points along this pathophysiological cascade presents a promising opportunity to slow atherosclerotic progression and mitigate the growing incidence of ischemic heart disease, particularly in rapidly developing regions such as SEAR.

METHODS

This review article aims to provide a comprehensive overview of the pathophysiological mechanisms underlying atherosclerosis and to summarize current and emerging strategies for its prevention. A literature search was performed using PubMed, Google Scholar, and ScienceDirect, including studies published in English that addressed the mechanisms, risk factors, and preventive interventions for atherosclerosis. The selected literature was analyzed descriptively and thematically to elucidate the sequential processes of atherosclerotic development and the mechanisms by which various preventive strategies may attenuate disease progression.

RESULTS

Overview of Atherosclerosis Pathophysiology

Atherosclerosis develops through a complex, multistep process, beginning with endothelial dysfunction and progressing to plaque formation and potential rupture. Disturbances in blood flow generate mechanical stress that compromises endothelial integrity, facilitating the infiltration and modification of low-density lipoproteins (LDL) within the vascular intima. This lipid accumulation triggers an inflammatory response, promoting endothelial activation and recruitment of immune cells, ultimately leading to the formation of foam cells. The aggregation of foam cells contributes to the development of atherosclerotic plaques, which are subsequently capped by a fibrous layer. Under certain conditions, the fibrous cap may rupture, resulting in thrombus formation and obstruction of blood flow. Such vascular occlusion can precipitate clinical events, including myocardial infarction, due to impaired myocardial perfusion [3,4], as depicted in **Figure 1**.

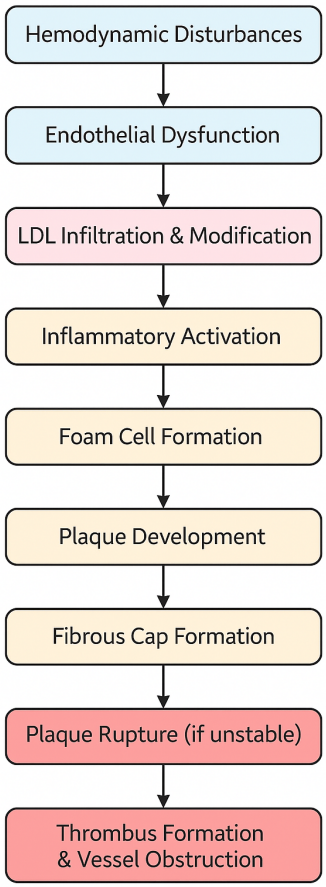

Figure 1. Overview of the atherosclerosis pathophysiology from endothelial dysfunction to plaque rupture and thrombosis.

Endothelial Dysfunction

Disruption of vascular homeostatic regulation leads to endothelial dysfunction, resulting in vascular constriction, lipid infiltration and modification, inflammatory activation, leukocyte adhesion, platelet aggregation, and ultimately atherosclerotic plaque formation [4]. Hemodynamic disturbances serve as key predisposing factors for endothelial injury; alterations in laminar flow, such as separation, recirculation, reattachment, or turbulence, can induce mechanical stress on the vessel wall, compromising endothelial integrity. This facilitates lipid entry into the intimal layer and promotes the expression of pro-atherogenic endothelial genes, including monocyte chemoattractant protein-1 (MCP-1), platelet-derived growth factors (PDGFs), and platelet endothelial cell adhesion molecule-1 (PECAM-1), among others, thereby accelerating plaque development [3].

Reduced bioavailability of nitric oxide (NO) also plays a critical role in atherogenesis. As a potent vasodilator, NO maintains endothelial-dependent relaxation of vascular smooth muscle and exerts anti-atherogenic effects by inhibiting platelet aggregation, oxidative stress, inflammation, and thrombogenic factor activation. However, cardiovascular risk factors that increase oxidative stress, such as hypertension, diabetes mellitus, smoking, and hyperlipidemia, impair NO synthesis. Oxidative stress, in turn, enhances the production of pro-atherogenic cytokines including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6); chemokines such as MCP-1; and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), further suppressing NO bioavailability [3]. Consistently, several studies have reported impaired endothelium-dependent vasodilation in patients with hypercholesterolemia and hypertension [5–7].

LDL Internalization and Modification Inside the Tunica Intima

Disturbed blood flow and endothelial injury facilitate the infiltration of lipoproteins, particularly low-density lipoprotein (LDL), into the vascular intima. Once retained within the subendothelial space, LDL undergoes oxidative modification mediated by reactive species such as superoxide anions, hydroxyl radicals, phospholipases, and lipoxygenases. These oxidative processes, driven by endothelial cells and macrophages, generate oxidized LDL (oxLDL), a potent pro-inflammatory molecule that plays a central role in initiating and propagating atherosclerotic plaque formation [3,4].

Inflammation and Endothelial Activation

Oxidized low-density lipoprotein (oxLDL) stimulates the expression of various pro-inflammatory mediators, including IL-1, TNF-α, advanced glycation end products (AGEs), and modified lipoproteins. These mediators initiate type I endothelial activation, an acute response characterized by alterations in vascular tone, increased leukocyte adhesion and transmigration (diapedesis), and enhanced vascular permeability. When sustained, this inflammatory response progresses to type II endothelial activation, a more chronic and complex stage driven by the activation of nuclear factor kappa B (NF-κB). Activation of NF-κB upregulates the expression of adhesion molecules such as VCAM-1 and ICAM-1, as well as chemokines including MCP-1 and IL-8. This process is further accompanied by the induction of prothrombotic mediators, including plasminogen activator inhibitor (PAI-1) and tissue factor, amplifying vascular inflammation and promoting atherogenesis [3], as described in **Figure 2**.

Monocyte Recruitment and Foam Cell Development

During endothelial activation, MCP-1 plays a pivotal role in mediating monocyte recruitment and transmigration across the endothelium. Facilitated by P-selectin, circulating monocytes are initially captured and undergo rolling interactions along the activated endothelium. Firm adhesion is subsequently achieved through the engagement of monocyte integrins with endothelial adhesion molecules such as ICAM-1 and VCAM-1. Endothelial-bound chemokines—including CXCL1, CXCL2, CXCL4, and CXCL5—further activate monocytes and promote their transendothelial migration into the tunica intima [3].

Within the intima, monocytes differentiate into macrophages, which can adopt either a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype. Under atherogenic conditions, polarization favors the M1 macrophage, characterized by the secretion of inflammatory cytokines and chemokines, as well as the generation of reactive oxygen species (ROS). These processes amplify local inflammation and enhance recruitment of additional monocytes [3].

Macrophages internalize both modified and unmodified LDL, further exacerbating lipid accumulation within the intima. Excess oxLDL not only augments its own uptake through scavenger receptors but also perpetuates inflammatory signaling via NF-κB activation. This signaling cascade sustains endothelial activation, monocyte infiltration, and foam cell formation, contributing to progressive lesion expansion [3,4].

Moreover, intracellular cholesterol overload promotes the formation of cholesterol crystals, which trigger NLRP3 inflammasome activation, driving additional pro-inflammatory cytokine release and ROS generation. Together, these mechanisms establish a self-reinforcing cycle of inflammation, lipid accumulation, and tissue injury that accelerates atherosclerotic plaque development [3,4].

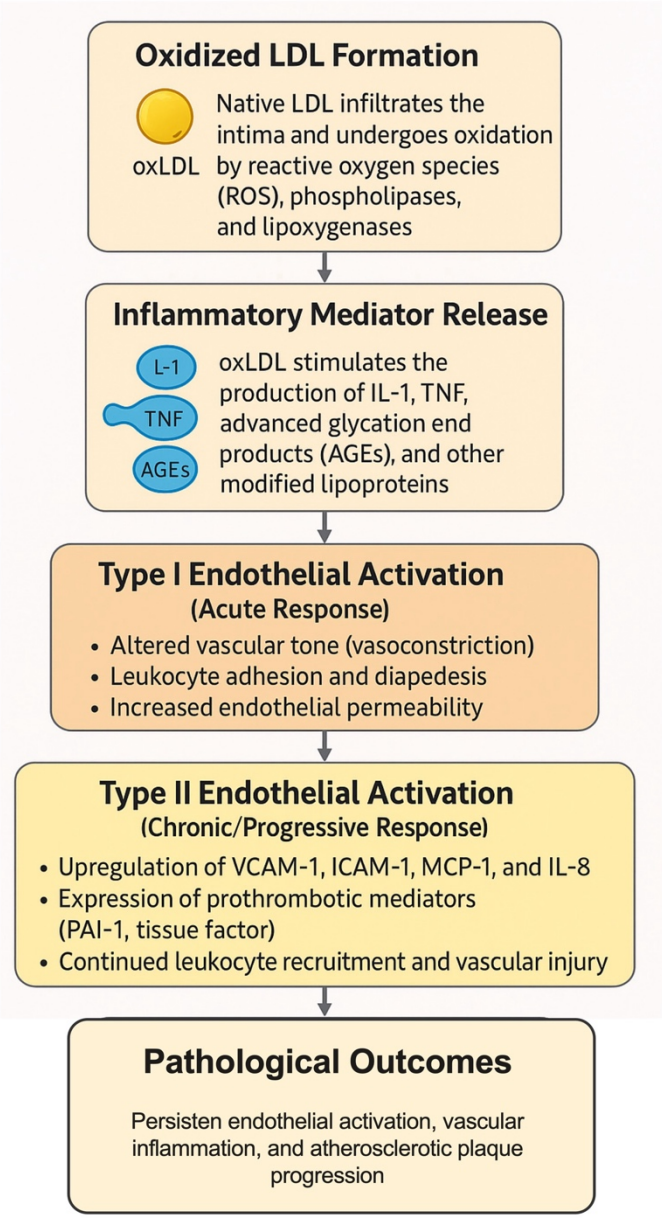

Figure 2. Endothelial Activation Cascade Induced by Oxidized LDL

Fibrous Cap Formation and Plaque Stabilization

The progression of atherosclerosis involves the transition of fatty streaks into fibroatheromatous plaques, characterized by the development of a necrotic core, a cell-depleted, lipid-rich region within the intima. This necrotic core is overlaid by a fibrous cap composed primarily of collagen and extracellular matrix proteins synthesized by vascular smooth muscle cells. The formation of this cap serves to stabilize the atherosclerotic plaque and marks the evolution toward an advanced lesion [3,4].

Atherosclerosis Plaque Rupture and Myocardial Infarction

Hemodynamic forces, particularly shear stress, play a central role in plaque destabilization and rupture. When a plaque fissures or ruptures, its highly thrombogenic contents, especially the lipid core and exposed subendothelial collagen, come into direct contact with circulating blood, initiating the coagulation cascade. Platelets are rapidly attracted to the site of injury, where they adhere to exposed collagen, become activated, and aggregate to form a hemostatic plug [3].

Activated platelets release prothrombotic and inflammatory mediators that amplify aggregation and recruit additional platelets to the site. Concurrently, tissue factor released from the ruptured plaque interacts with plasma factor VII, triggering a series of enzymatic reactions culminating in the generation of thrombin. Thrombin then catalyzes the conversion of fibrinogen to fibrin, forming a stable fibrin-platelet network over the lesion. During this reparative process, activated platelets secrete transforming growth factor-beta (TGF-β), which stimulates interstitial collagen synthesis and contributes to fibrous cap thickening. However, excessive fibrin deposition and cap expansion can further narrow the coronary lumen, ultimately obstructing blood flow and leading to myocardial infarction [3,4].

DISCUSSION

Primary Prevention to Mitigate the Coronary Events

Dietary Nitrate and Its Protective Effects in Atherosclerosis

Dietary nitrates, have been increasingly recognized for their vasculoprotective and anti-atherosclerotic properties. Experimental studies have demonstrated that nitrate supplementation markedly reduces atherosclerotic lesion area in vivo [8] and is associated with lower mortality from atherosclerotic vascular diseases [9]. Furthermore, dietary nitrate intake has been shown to attenuate the progression of atherosclerotic plaque formation [10].

Dietary nitrate, which is abundant in beetroot and leafy green vegetables, serves as a precursor for nitric oxide (NO) through the enterosalivary nitrate–nitrite–NO pathway, representing a significant alternative mechanism for NO production. In this pathway, NO is generated via the stepwise reduction of nitrate and nitrite anions, facilitated by facultative anaerobic bacteria located on the dorsal surface of the tongue, the acidic conditions of the stomach, and various endogenous molecules capable of reducing nitrite. Notably, this nitrate–nitrite–NO pathway operates independently of nitric oxide synthase (NOS) and may be particularly active under hypoxic conditions [9].

The underlying mechanisms for these benefits are multifactorial. Since oxLDL plays a pivotal role in triggering endothelial dysfunction and atherogenesis, dietary nitrates exert protection primarily through their antioxidant and anti-inflammatory actions. Nitrate-derived NO suppresses oxidative stress and lipid oxidation, thereby preserving endothelial integrity and vascular homeostasis [8].

In addition, dietary nitrates modulate inflammatory pathways by inhibiting monocyte-derived inflammatory mediators and enhancing anti-inflammatory cytokine expression, particularly IL-10. Nitrates also reduce leukocyte rolling and adhesion to the endothelium, further limiting vascular inflammation and plaque initiation [10]. Collectively, these mechanisms highlight dietary nitrate as a promising nonpharmacologic strategy to prevent or slow atherosclerosis progression.

Benefits of Statins for Atherosclerosis Prevention

Statins provide multifaceted benefits in the prevention and management of atherosclerosis. In patients with acute coronary syndrome, statin therapy can reduce atherosclerotic plaque volume by up to two-fold [11]. As HMG-CoA reductase inhibitors, statins increase hepatic LDL receptor expression, enhancing LDL clearance from circulation and reducing its retention in the endothelium, thereby limiting plaque formation [12,13]. Beyond lipid-lowering, statins preserve endogenous antioxidant activity to prevent LDL oxidation, inhibit macrophage uptake of LDL, and suppress monocyte adhesion to the endothelium, collectively reducing foam cell development and plaque progression [14–16].

Statins also improve endothelial function by upregulating endothelial nitric oxide synthase (eNOS), maintaining nitric oxide bioavailability, and inhibiting vascular smooth muscle cell migration and proliferation, which limits new lesion formation [17–19]. In addition, statins exert antithrombotic effects by decreasing tissue factor expression in macrophages and reducing platelet reactivity, mitigating the risk of thrombosis associated with plaque rupture in acute coronary syndromes [13,20,21].

The Role of Antioxidants in Suppressing Atherosclerosis Formation

Oxidized LDL plays a central role in triggering inflammation and promoting atherosclerotic plaque development. Consequently, antioxidants such as tocopherol, ascorbic acid, and omega-3 fatty acids have been investigated for their potential to inhibit plaque progression [3].

Tocopherol, a fat-soluble vitamin, exhibits potent antioxidant properties and plays a critical role in atherosclerosis prevention, as low serum levels of α-tocopherol have been associated with increased atherosclerotic burden and coronary lesions [22]. Beyond its antioxidant activity, tocopherol exerts anti-inflammatory effects by suppressing the release of pro-inflammatory cytokines and pro-atherogenic chemokines, including IL-1β, IL-6, TNF-α, and IL-8, potentially through downregulation of NF-κB signaling [23–25]. Tocopherol further contributes to atherosclerosis prevention by reducing monocyte adhesion to the endothelium, thereby limiting foam cell formation and plaque development [24].

Ascorbic acid, a water-soluble vitamin with antioxidant properties, has similarly demonstrated efficacy in preventing plaque formation in both the aorta and coronary arteries [26]. Its protective effects involve the inhibition of LDL oxidation, reduction of monocyte-endothelial adhesion, and preservation of endothelial function. Specifically, ascorbic acid decreases monocyte recruitment by downregulating MCP-1 expression, enhances superoxide dismutase (SOD) activity to limit LDL oxidation, and increases nitric oxide production to counteract endothelial dysfunction [27].

Omega-3 fatty acids are well-recognized for their anti-inflammatory properties [28]. In patients with coronary artery disease, supplementation with omega-3 in addition to statin therapy has been shown to prevent coronary plaque progression [29]. Omega-3 fatty acids reduce the release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 and inhibit monocyte adhesion to the endothelium by downregulating VCAM-1 and CXCL expression, thereby mitigating atherosclerosis progression [28,30].

CONCLUSIONS

Atherosclerosis is a multifactorial process initiated by endothelial dysfunction, LDL oxidation, and chronic inflammation, ultimately resulting in plaque formation and potential rupture. Various interventions, including statins, dietary nitrates, and antioxidants such as tocopherol, ascorbic acid, and omega-3 fatty acids, have demonstrated efficacy in slowing atherosclerosis progression through their antioxidant, anti-inflammatory, and endothelium-preserving effects. These strategies highlight the importance of both pharmacological and nutritional approaches, alongside risk factor management, as integral components of atherosclerosis prevention.

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