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Understanding Atherosclerosis: Pathogenesis, risk Factors, and treatment approaches

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Abstract. Atherosclerosis is a prevalent and severe disease in modern medicine, as it significantly influences contemporary society, contributing to high morbidity and mortality rates. The pathogenesis of atherosclerosis includes six critical steps: endothelial dysfunction, oxidative stress, inflammatory response, formation of fatty streaks, plaque progression, as well as plaque maturation and complications. Current treatments for atherosclerosis encompass lifestyle modifications, pharmacological interventions, and surgical procedures. This study calls for optimal solutions for atherosclerosis treatment, with the hope that future advancements will address these shortcomings and improve patient outcomes.

Keyword: Atherosclerosis, pathogenesis, treatments.

1. Introduction

The concept of atherosclerosis originates from the Greek language which means ‘gruel’ or ‘porridge’, referring to the accumulation of the lipid found in the center of a typical atherosclerotic plaque or atheroma [1]. In modern medicine, owing to the diversity in research perspectives and academic backgrounds, different medical communities offer varied interpretations of atherosclerosis. For example, from an epidemiological standpoint focusing on the distribution and determinants of atherosclerosis in populations, atherosclerosis is defined as a chronic disease identified by fatty deposits, inflammatory cells, and fibrous elements in arteries with the impact of lifestyle and environmental factors, such as smoking, obesity [2]. Moreover, a case study perspective examines atherosclerosis through the progression of the disease in individual patients. This chronic condition is initiated by endothelial dysfunction, followed by a cascade of events which lead to vessel narrowing and activation of inflammatory pathways, and ultimately turns into the formation of atheroma plaques [3]. In addition, geneticists conceptualize atherosclerosis as a complex disease affected by genetic as well as environmental factors. They assert that genetic factors are pivotal in the susceptibility to atherosclerosis, when some specific genes and genetic variations resulting in the disease’s development and progression [4]. From the interpretations provided above, it is evident that research from various perspectives shares many commonalities that atherosclerosis refers to a situation with narrowed and hardened arteries due to construction of plaque, establishing a solid theoretical foundation and practical framework for the study of atherosclerosis.

Currently, atherosclerosis has emerged as one of principal sources of morbidity and mortality globally, with its prevalence exhibiting an upward trend in the past twenty years [5]. In 2000, the global population affected by carotid atherosclerosis was approximately 677 million. However, by 2020, the

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global prevalence had escalated to an estimated 27.6%, equating to approximately 1.067 billion individuals [6]. A series of diseases triggered by atherosclerosis, such as coronary artery disease, vascular dementia, erectile dysfunction, or limb loss, can jeopardize individual health, impact quality of life, and even bring life-threatening problems [7]. Beyond individual health, atherosclerosis also negatively influences the overall economic development of countries with its direct and indirect costs [8]. Take healthcare systems as an example. The direct costs associated with diagnosis, treatment, hospitalization, and rehabilitation contribute significantly to healthcare expenditures in various countries. A study conducted in Sweden reveals that the annual medical cost for patients with atherosclerosis was €6923, compared to €2699 for other cardiovascular diseases [9]. While considering indirect costs, atherosclerosis adversely affects the workforce in labor market, as this chronic illness leads to reduced work participation, increased absenteeism, and lower productivity, thereby impeding economic growth. Indirect costs, such as absenteeism due to illness, account for 60% of the annual total cost for patients with atherosclerosis [10]. Furthermore, the risk of early retirement for these patients is three times higher than that of their healthy peers [11]. Thus, from a socioeconomic perspective, atherosclerosis imposes significant negative impacts, as the direct and indirect costs associated with treating atherosclerosis, including medical expenses and productivity losses, place a substantial financial burden on individuals and societies at large.

Consequently, academic research on this disease is indispensable. This study targets at exploring existing treatment modalities to mitigate the impact of atherosclerosis on individual and economic development comprehensively. By doing so, the study seeks to alleviate the burden on patients and their families, enhance work productivity, and improve overall quality of life. Furthermore, this research endeavors to provide valuable insights and recommendations for future therapeutic strategies and public health policies.

2. Mechanism

As previously discussed, despite the diverse research perspectives on atherosclerosis, there are numerous commonalities in the findings concerning its mechanism. Generally speaking, the pathogenesis can be divided into the following steps:

2.1. Step One: Endothelial Dysfunction

Atherosclerosis typically commences with destruction to the endothelium, the inner lining of the arteries. This destruction could be triggered by various elements, including hypertension, hypercholesterolemia, smoking, diabetes, and inflammation. When being injured, the endothelium is unable to control vascular tone, restrain smooth muscle cell proliferation, and suppress inflammatory responses [12].

Furthermore, endothelial injury disrupts the tight connections between endothelial cells. This disruption compromises the endothelial barrier function, thereby facilitating the permeability of lipoproteins, particularly low-density lipoprotein (LDL). Consequently, the lipoproteins can traverse the endothelium and infiltrate the arterial wall [13].

2.2. Step Two: Oxidative Stress

The second step relates to lipoprotein infiltration, as LDL particles penetrate the intimal layer of the arteries through blood circulation. When endothelial cells are destroyed or dysfunctional, vascular permeability increases, which facilitates the penetration of LDL particles into the intimal layer. This infiltration process is influenced by factors, embracing hyperlipidemia, diabetes, smoking, and hypertension [14].

Then, oxidative stress appears, initially driven by reactive oxygen species (ROS) which mainly originate from the mitochondrial respiratory chain, NADPH oxidase, xanthine oxidase, together with nitric oxide synthase. These ROS oxidize LDL, forming oxidized LDL. Oxidized LDL (OXLDL) is subsequently replaced by macrophages, generating foam cells. Subsequently, cells pile up in the arterial wall, resulting in plaques. With influence of oxidative stress, cells release a series of cytokines and chemical mediators, including tumor necrosis factor, interleukin-1β, interleukin-6, as well as monocyte chemoattractant protein-1. These factors play crucial roles in inflammatory responses and cellular damage, further facilizing the development of atherosclerosis [15].

2.3. Step Three: Inflammatory Response

OXLDL participates in initiating the recruitment of immune cells, especially monocytes, to inflamed regions. This process starts when OXLDL is recognized by endothelial cells lining the arterial walls, leading to the enhancement of adhesion molecules including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 [16]. These adhesion molecules accelerate the adhesion of circulating monocytes to the endothelium.

Upon adhesion, monocytes transmigrate into the intimal layer of the artery through a process known as diapedesis [17]. In the intima, monocytes evolve into macrophages under the impact of local cytokines and growth factors. These macrophages subsequently engulf OXLDL via scavenger receptors, thereby transforming into lipid-laden foam cells.

2.4. Step Four: Formation of Fatty Streaks

The aggregation of foam cells constitutes a crucial phase in the pathogenesis of atherosclerosis. Foam cells initiate when macrophages internalize OXLDL particles via scavenger receptors. These lipid-laden macrophages, now designated as foam cells, amass in the intimal layer of the arterial wall. This accumulation signifies the earliest discernible lesion of atherosclerosis, referred to as a fatty streak. Fatty streaks are concerned as the incipient stage of plaque formation [18].

As foam cells aggregate, they engender a microenvironment replete with lipids and inflammatory mediators. The presence of foam cells within the intima is not merely a passive occurrence; these cells are metabolically active and lead to the advancement of the lesion. Foam cells secrete an array of pro-inflammatory cytokines and chemokines, recruiting immune cells to the lesion area. This recruitment of immune cells further worsens the inflammatory response as well as fosters the expansion of the plaque.

Foam cells secrete a diverse array of pro-inflammatory cytokines and chemokines, embracing tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6. These cytokines potentiate local inflammatory response by recruiting additional immune cells, as T-lymphocytes and monocytes, to the lesion area [19]. This recruitment establishes a positive feedback loop that perpetuates inflammation and facilitates the progression of the atherosclerotic plaque.

In addition to cytokines, foam cells produce matrix metalloproteinases (MMPs), decreasing the extracellular matrix and facilitate the remodeling of the arterial wall [20](Simões et al., 2022). This remodeling can result in the attenuation of the fibrous cap overlying the lipid core, rendering the plaque more susceptible to rupture. Thus, it may lead to the exposure of thrombogenic material to the bloodstream, culminating in the formation of a thrombus and potentially precipitating acute cardiovascular events.

2.5. Step Five: Plaque Progression

At the beginning of plaque formation, smooth muscle cells (SMCs) from the media layer of the arterial wall shift to the intima. Once within the intima, these SMCs proliferate, contributing to the thickening of the arterial wall.

The migrated and proliferated SMCs synthesize extracellular matrix (ECM) components, comprising collagen, elastin, and proteoglycans [21]. These ECM components constitute the structural framework of the plaque, especially the fibrous cap that overlays the lipid core. The fibrous cap imparts stability to the plaque, mitigating the risk of rupture. Nevertheless, the continuous synthesis of ECM might lead to the growth and expansion of the plaque as well, thereby narrowing the arterial lumen and impeding blood flow.

As foam cells within the atherosclerotic plaque experience apoptosis or necrosis, they secrete their lipid content into the extracellular matrix. This liberated lipid accumulates and forms a necrotic core, a hallmark of advanced atherosclerotic lesions. The necrotic core comprises necrotic cells, lipids, and

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cellular debris, contributing to the overall instability of the plaque. A substantial necrotic core, coupled with a thin fibrous cap, exacerbates the risk of plaque rupture [22].

2.6. Step Six: Plaque Maturation and Complications

The fibrous cap is a crucial part of plaques which confers structural stability to the lesion. It functions as a barrier, segregating the lipid-rich necrotic core from the bloodstream. However, integrity of the fibrous cap is not assured. Chronic inflammation within the plaque can precipitate the degradation of extracellular matrix components by matrix metalloproteinases secreted by macrophages and other inflammatory cells. This degradation can attenuate the fibrous cap, rendering it easier to rupture [23]. A thin and vulnerable fibrous cap constitutes a significant risk factor for acute cardiovascular events.

As atherosclerotic plaques advance, they may undergo calcification, a process identified by the gathering of calcium deposits within the plaque. Calcification is a multifaceted process influenced by factors as inflammation, oxidative stress, and the presence of apoptotic cells. Over time, these calcium deposits can coalesce into large, rigid structures within the plaque, further augmenting arterial wall stiffness [24]. Calcified plaques are less likely to rupture compared to their non-calcified counterparts, yet they can still contribute to arterial rigidity and diminished elasticity. This arterial stiffness can result in increased blood pressure and impaired blood stream, subsequently exacerbating the risk of cardiovascular events.

Plaque rupture represents one of the most perilous complications of atherosclerosis. When the fibrous cap turns into attenuated, it may rupture, exposing the thrombogenic necrotic core to the bloodstream. This exposure initiates the coagulation cascade, culminating in the rapid formation of a thrombus [25]. The thrombus can partly or entirely occlude the artery, thereby obstructing blood flow to downstream tissues.

In short, atherosclerosis starts with endothelial damage triggered, as hypertension, hypercholesterolemia, smoking, diabetes, and inflammation. This damage increases the permeability of LDL into the arterial wall. Oxidative stress leads to the formation of OXLDL. These foam cells accumulate, creating fatty streaks and contributing to plaque formation. Chronic inflammation and matrix metalloproteinases (MMPs) degrade the extracellular matrix, thinning the fibrous cap and promoting the risk of plaque rupture. Calcification can also occur, leading to arterial stiffness and elevated blood pressure, further exacerbating cardiovascular risks.

3. Treatment

Regarding the aforementioned steps of the pathogenesis of atherosclerosis and its clinical manifestations, medical scientists and pathologists have proposed numerous treatment plans from different perspectives. By effectively integrating these plans, the following comprehensive treatment strategies can be derived, embracing lifestyle modifications, pharmacological interventions, and surgical procedures.:

3.1. Strategies One: Lifestyle modification

Lifestyle modification is regarded as one of the most fundamental, effective and least adverse-effect-prone strategy for preventing atherosclerosis. It can attenuate blood pressure and lipid levels, mitigate endothelial damage, alleviate psychological stress, and bolster immune function. Strategies to cultivate salutary lifestyle habits include smoking cessation, weight reduction, dietary modifications, increased physical activity and so on [26]. For example, smoking cessation can attenuate inflammatory markers and hypercoagulable states within the body, subsequently diminishing inflammation within the arterial walls. By reducing dietary fat intake, particularly saturated and trans fats, lower LDL cholesterol (LDL-C) levels occur, subsequently mitigating the risk of atherosclerosis. Additionally, it can enhance endothelial function, thereby improving the elasticity and overall health of blood vessels.

3.2. Strategies Two: Antioxidant therapy

Concerning the second step in the mechanism, oxidative stress, a specific class of pharmacological agents could be adopted to prevent oxidation. Antioxidant therapy is used to mitigate oxidative stress,

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an essential factor in the pathogenesis and development of atherosclerosis [27]. Oxidative stress emerges when there is a disproportion between the production of reactive oxygen species and the body's capacity to neutralize them with antioxidants. Elevated levels of ROS can lead to the formation of OXLDL. OXLDL is especially deleterious when promoting inflammation, endothelial dysfunction, and the development of plaques [28]. By attenuating oxidative stress, antioxidant therapy aids to reduce the formation of OXLDL, subsequently decelerating the progression of atherosclerosis.

Several antioxidant agents are commonly used in the management of atherosclerosis, such as vitamins E and C [29]. Take Vitamin E as an example. It is available in diversified formulations, as oral capsules, tablets, and liquid preparations. Additionally, as a water-soluble antioxidant, Vitamin C helps in the regeneration of vitamin E and neutralizes ROS in the aqueous compartments of the body. It is available in oral tablets, chewable tablets, and effervescent formulations. However, little documented research has been found using human subject. In an experiment, rabbits were fed 2100 milligrams of vitamin E. After 4 weeks, a cholesterol-lowering effect was observed, and after 8 weeks, cholesterol levels had decreased by approximately 50% [30].

3.3. Strategy Three: Anti-inflammatory drugs

Anti-inflammatory pharmacotherapy essentially manages atherosclerosis by inhibiting inflammatory responses, reducing the infiltration of inflammatory cells into the arterial wall, and decreasing the release of inflammatory mediators [31]. This therapeutic approach helps to decelerate the progression of atherosclerosis.

Globally, there are two primary classes of anti-inflammatory drugs used in this context. The first one is Tacrolimus [32]. This immunosuppressive agent functions by inhibiting the activity of T-lymphocytes, which are integral components of the immune response. By binding to the FK506-binding protein, tacrolimus inhibits calcineurin, a protein phosphatase involved in T-cell activation. This suppression of T-cell activity attenuates inflammation and modulates immune responses.

The second class, represented by Canakinumab, comprises IL-1β inhibitors. This monoclonal antibody targets interleukin-1 beta, a cytokine which makes a critical part in the inflammatory cascade [33]. By binding to IL-1β, canakinumab prevents its interaction with receptors, thereby mitigating inflammation. This mechanism is particularly advantageous in conditions where IL-1β is a predominant driver of inflammation. In Cantos trial, over a median follow-up period of 3.7 years, a 150mg dose of canakinumab administered every quarter significantly decreased the incidence of recurrent cardiovascular events. Differently, the primary endpoint event rate in the 150mg group was 3.86 events per 100 person-years (compared to 4.50 events in the placebo group) [34].

3.4. Strategy Four: Lipid-lowering drugs

Lipid-lowering drugs, also known as hypolipidemic agents, are pharmacological interventions designed to decrease lipid levels in the bloodstream, particularly LDL-C [35]. The basic class of medications currently in use are statins. Statins function by restraining the enzyme HMG-CoA reductase, which is pivotal in the hepatic synthesis of cholesterol. By inhibiting this enzyme, statins effectively reduce cholesterol production, resulting in decreased levels of LDL-C in the blood. Additionally, statins enhance the hepatic uptake of LDL-C, further lowering blood cholesterol levels.

A newer class of lipid-lowering drugs targets the protein PCSK9 [36]. PCSK9 combines with LDL receptors on hepatocytes and enhances their degradation. By restraining PCSK9, this medicine adds the availability of LDL receptors to clear LDL-C from the bloodstream, thereby reducing cholesterol levels. Examples of PCSK9 inhibitors include alirocumab and evolocumab.

3.5. Strategy Five: Surgery

The final approach to treating atherosclerosis involves surgical interventions to open the arteries or remove plaque. Angioplasty is a minimally invasive procedure employed to dilate obstructed or narrowed arteries [37]. This procedure is frequently operated to restore myocardial perfusion without necessitating open-heart surgery. The procedure includes three primary steps: catheter insertion, balloon inflation, and stent placement. At first, a catheter is put into a blood vessel, typically the groin and wrist. It is then navigated through the vasculature to the site of the arterial occlusion. Upon reaching the stenotic segment, a small balloon at the catheter's tip is inflated. This balloon compresses the atheromatous plaque against the arterial walls, thereby widening the artery and enhancing blood flow. In most instances, a stent is deployed during the same procedure. A stent is a small, expandable metal mesh tube that maintains arterial patency after balloon deflation and catheter removal.

In addition to angioplasty, coronary artery bypass grafting (CABG) is another surgical intervention adopted to address coronary artery stenosis or occlusion due to atherosclerosis. The primary objective of CABG is to augment myocardial blood flow, thereby alleviating symptoms, which reduces the risk of myocardial infarction, and improving overall cardiac function.

During CABG, a surgeon constructs a bypass around the obstructed or narrowed coronary artery segments using a vascular graft. The graft is typically harvested from the patient's own body. The surgeon anastomoses one side of the graft to the aorta and the other side to the coronary artery distal to the obstruction. This allows blood to circumvent the blockage, ensuring an adequate supply of oxygenated blood to the myocardium.

4. Conclusion

This study discusses the term “atherosclerosis” and its definition in modern medicine as a disease identified by the formation of plaques within the arteries, resulting in a narrowing of the arterial diameter and impaired blood flow. Atherosclerosis has a significant impact on contemporary society. It is connected to high morbidity and mortality rates, imposing substantial burdens on the families of affected individuals, reducing their work capacity and participation, and negatively affecting both the patients themselves and the entire healthcare system.

The mechanism of atherosclerosis comprises of six steps, including endothelial dysfunction, oxidative stress, inflammatory response, formation of fatty streaks, plaque progression and plaque maturation and complications. There are numerous factors leading to this disease. Notably, smoking is a major risk factor, as it damages the endothelium, increases blood pressure, and reduces oxygen delivery to tissues.

Regarding atherosclerosis and its current treatments, including lifestyle changes, various medications, and surgical interventions. Antioxidant therapy can be effective against oxidative stress. Anti-inflammatory drugs can reduce the entry of inflammatory factors into the arterial walls, thereby reducing the likelihood of plaque formation. Lipid-lowering drugs work by inhibiting the HMG-CoA enzyme, which lowers the level of LDL in the blood. Physical surgery involves placing stents to support the arterial walls or selecting alternative vascular routes to alleviate the blockage caused by plaques.

However, there are still many shortcomings in the treatment of atherosclerosis, such as the inability to detect it in advance, the lack of corresponding drug treatments for plaque formation and dissolution, the inability to reduce treatment costs, and the impact on the patient, their family, and society. Due to space limitations, this study is currently unable to find the optimal solution for its treatment. However, we hope that in the near future, better solutions for atherosclerosis will emerge. This will also be the goal that more scientific researchers strive for.

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