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A Review Article on Atherosclerosis

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Abstract

The reduction of infectious diseases that affect children and young adults is largely responsible for rise in life expectancy. Our population is ageing, and chronic infectious diseases, particularly those of the cardiovascular system, are becoming increasingly prevalent. Arteriosclerosis causes an artery to stiffen. The three recognised lesions are atherosclerosis, Monckeberg medial calcific sclerosis, and arteriolosclerosis, and each has a unique origin, clinical course, and pathological effects. The most common cause of death is arteriosclerosis. Many studies have been done to identify and measure the risk factors for this disease. In essence, many of these studies have advanced our knowledge of the causes of arteriosclerosis, including high-cholesterol diets, hypertension, smoking, and inactivity. In addition to genetic dyslipidemia, hypertension, and diabetes, environmental risk factors like diet, smoking, stress, and a sedentary lifestyle can affect the development of atherosclerosis. Protective factors associated with parasite infestations and environmental disorders may also have an impact. Peripheral artery disease (PAD) is now more prevalent throughout the world. Limited pain-free walking distance (intermittent claudication) or tissue ulceration are two signs that PAD should be treated. Endovascular therapy has replaced open surgical surgery as the preferred type of treatment in many arterial regions because it is less intrusive. There is still no mention of treating the common femoral artery (CFA) in this. It is widely established that the presence of obstructive coronary lesions like angina or myocardial infarction is clinically correlated with the blood level of low-density lipoprotein (LDL) cholesterol.

Key Words: Peripheral artery disease, Angina, Atherosclerosis, Ischemia.

Introduction

The most prevalent causes of death in the industrialised world are coronary heart disease and cerebrovascular illness, both of which are primarily brought on by arteriosclerosis **[1].** An artery hardens due to arteriosclerosis. Atherosclerosis, Monckeberg medial calcific sclerosis, and arteriolosclerosis are the three known lesions, and they differ in terms of pathogenesis, clinical outcomes, and pathological repercussions. **[2-4].**

i. Atherosclerosis: The intimal lesions known as atheromas, atheromatous plaques, or fibrofatty plaques, which protrude into and get stuck in arterial lumens and weaken the underlying media, are the most common and significant pattern. They might trigger significant complications. The atheroma is the distinctive lesion in atherosclerosis. With varying volumes and types of lipids, connective tissues, inflammatory cells, and a range of extracellular components, such as calcium deposits, matrix proteins, and enzymes, atherosclerotic lesions increase the artery intima. **[5-7].** Since atherosclerosis is the leading cause of death in industrialised nations, extensive research has been done on this lesion, leading to significant advancements in our knowledge of its pathogenesis, risk factors, natural history, treatment, and prevention.

   Although "athero" literally means "gruel like," sclerosis denotes hardening. As a result, the literal definition of atherosclerosis is the thick, chunky liquid that hardens the arteries. Atheromatous arteriomalacia or atheromatous arteriopathy are possible alternative names for some of the lesions. But because they have developed into semantically distinct terms, historically these have been referred to as sclerotic lesions rather than hard lesions. Additionally, a term's definition frequently deviates semantically from its Greek origin. Even though the word "hippocampus" is Latin for "sea horse," we recognise that this historical name should not be taken literally. Additionally, other pathologies such as multiple sclerosis and hippocampal sclerosis, in which hardening is not the distinguishing change, are frequently referred to as having sclerosis. This makes it easy to recognise atherosclerosis as a respectable subtype of arteriosclerosis. **[8].**

ii. Monckeberg medial calcific sclerosis: As the name suggests, Monckeberg medial calcific sclerosis is a calcification condition that affects the media of large and medium-sized arteries. According to reports, people under 50 are infrequently diagnosed with it. Monckeberg calcific lesions, according to our German translators, exclusively affect the tunica media of arteries, not the arterial lumen. **[9].** The term Monckeberg medial calcific sclerosis (MMCS) is probably only partially accurate, because there are different

types of vascular calcification. **[10,11].** Activation and migration of myofibroblasts from the adventitia as well as differentiation of smooth muscle cells are two possible pathways that may be involved in MMCS. Age, diabetes mellitus, and chronic kidney disease (CKD) are the specific clinical conditions connected to MMCS. MMCS is uncommon before the age of 50 in general, but it may have started sooner in CKD even in the absence of atherosclerotic plaques. A kind of vascular calcification (VC) known as Monckeberg medial calcific sclerosis has been linked to higher rates of cardiovascular morbidity and mortality. Both types of VC can present intraoperative challenges during vascular surgery, even though MMCS does not have an obstructive aspect, in contrast to advanced atherosclerotic lesions. **[12].**

iii. Arteriolosclerosis: It is a lesion of arterioles, which are small arteries having one or two layers of smooth muscle cells. Arteriolosclerosis affects arterioles all over the body and is frequently linked to both high blood pressure and diabetes. The hyperplastic type and the hyaline type of arteriolosclerosis are two histologically distinct yet unquestionably linked subtypes. **[13].** The subtype "fibromuscular intimal thickening" would also include fibromuscular hyperplasia in arteries, which is seen in transplant vasculopathy, restenosis lesions after balloon angioplasty or stenting, and nonspecific intimal thickening that develops in temporal arteries with ageing. Hyalinosis primarily affects arterioles, however arteries can also experience the same alterations. As a result, calling these lesions simply "intimal hyalinosis" would encompass similar abnormalities in both arteries and arterioles. **[14,15].**

These lesions commonly have three things in common. Both the stiffening of arterial arteries and the thickening of the arterial wall were formerly thought to be "degenerative" disorders. **[16]**.

Epidemiology of Arteriosclerosis:

Cardiovascular diseases (CVD) are the leading cause of mortality in the Western population **[17].** Atherosclerosis is considered a progressive inflammatory systemic disease affecting mainly the wall of large and medium arteries, such as the aorta, carotid, and coronary arteries **[18, 19]**, at sites prone to low, turbulent, or oscillatory shear stress, like branches, curvatures, or bifurcations [20]. Although clinically relevant lesions become evident in middle-aged adults, it has been demonstrated that fat accumulation (known as fatty streaks) begins in early childhood **[21].** The latency period is long, and clinical manifestations become evident several years later **[22].**

Cardiovascular (CV) risk factors such as hypercholesterolemia, hyperglycaemia, obesity, hypertension, smoking, and aging promote vascular inflammation and endothelial activation **[23-25].** Controlling these factors reduces the risk of acute vascular complications and death from CVD [17]. In accordance with the latest report of the World Health Organization (WHO), deaths from noncommunicable diseases account for almost 74% and they are mainly attributed to CVD **[26].** The incidence of target organ damage associated to CVD increases with age, and gender studies show global higher incidence in men for stroke and coronary artery disease (CAD) [26]. The global mortality rate for CVD has significantly decreased in the last years; however, stroke and CAD remain the leading causes of mortality for CVD in adults **[26].**

Oxidation of low-density lipoprotein (LDL) cholesterol is crucial in the development of atherosclerosis, and low LDL levels reduce the risk of major events in patients with CVD [6]. Despite that macrophages have low affinity for nonoxidized LDL, reducing LDL levels prevents oxidation, as recognized by European and American cardiac societies in their guidelines **[27].** Besides the importance of this process, oxidation of LDL is not the sole initiator of inflammation, as the imbalance between oxidants and antioxidants is also important for the process of atherogenesis.

Causes of Arteriosclerosis

In the World, arteriosclerosis is the leading cause of death. The risk factors for this illness have been the subject of much research to identify and quantify them. In essence, a lot of these studies have helped us understand the role that high-cholesterol diets, hypertension, smoking, and inactivity play in the aetiology of arteriosclerosis **[28, 29].**

Diabetes and Smoking

Compared to non-diabetics, people with diabetes experience arteriosclerosis obliterans (ASO) more frequently and at a younger age, and their condition affects their legs more widely **[30, 31].** Diabetes patients who get ASO frequently experience ischemia, claudication, ulceration, and gangrene as a result. Different risks apply to diabetics who are being treated with insulin, sulfonylurea, or diet, depending on certain parameters, particularly plasma lipoprotein **[32].** In all types of diabetes mellitus, hypertension and cigarette smoking appear to be significant risk factors for the onset of peripheral arteriosclerosis. In the continuing investigation, occlusive peripheral artery disease was present in about 30% of the diabetic partients **[33].** The prevalence of ASO was significantly influenced by age, according to an analysis of the risk factors. The other risk variables that were shown to be most important included smoking and hypertension,

which are both known to be linked to arteriosclerosis obliterans in non-diabetic subjects. In the current study, a history of smoking was almost necessary for the emergence of severe ASO. Smokers with diabetes who were on a diet had the highest incidence of severe arteriosclerosis obliterans (SASO). Despite having equal fasting glucose levels, the SASO prevalence was lower in the group of participants on antihyperglycemic medications than in the group receiving diet therapy, and it was lower in that receiving insulin therapy than in those receiving oral sulfonylurea therapy **[34].**

Homocystinuria

Homocystinuria is a genetically recessive disease that only affects one in 80,000 people, making it a highly uncommon risk factor for arteriosclerosis. While in general this would be regarded as a negligible portion of the population, this is not the case for heterozygotes, whose rates are estimated to range from 0.5 to 1.5% in diverse communities. By the age of 50, heterozygotes for cystathionine synthase deficiency may be considerably more likely to develop coronary artery disease **[35].** It is a hereditary disorder characterised by a deficit in the enzyme hepatic cystathionine synthase. Methionine, an amino acid found in proteins, is usually used to make homocysteine. Since it is quickly transformed into cystathionine, which is required in other metabolic processes. It is regarded as a hazardous intermediate. Homocystinuria prevents individuals from effectively converting homocysteine to cystathionine, which results in higher homocysteine levels. It affects aberrant cellular proliferation in blood vessels and make the normally thin cellular linings of the walls extremely permeable. It is believed that these changes in cellular function serve as the starting point for later arteriosclerotic modifications. In addition to the medical worry over homocystinuria heterozygotes' potential risk of developing cardiovascular disease (CVD), it has been hypothesised that diets deficient in vitamin B may also be a risk factor. It is likely that this vitamin facilitates the conversion of homocysteine to cystathionine. Since vitamin B deficiency is associated with an increased risk of developing arteriosclerosis. Additionally, after three weeks on a reduced vitamin B diet, people started excreting homocysteine. Diets high in meat and dairy products, also linked to an elevated risk of cardiovascular disease (CVD), have methionine-to-vitamin B6 ratios that are significantly greater than those found in fruits and vegetables **[36]**.

Environmental factor

Arteriosclerosis is influenced by environmental risk factors such as nutrition, smoking, stress, and a sedentary lifestyle, in addition to inherited dyslipidemia, hypertension, and diabetes. It might also be influenced by protective factors related to environmental illnesses and parasite infestations **[37].** The risk factors for arteriosclerosis have been the subject of extensive research to identify and quantify them. In essence, a lot of these studies have helped us understand the role that high-cholesterol diets, hypertension, smoking, and inactivity play in the aetiology of arteriosclerosis. that the development of arteriosclerosis may be influenced by hereditary and dietary variables that greatly raise plasma homocysteine concentrations **[38,39].**

Animal models exposed to CO for an extended period below the lethal dose may develop atherosclerotic alterations **[40],** including heart deterioration and sclerotic changes in the aorta arteries. Continuous exposure to low levels of CO causes hypercholesterolemia, cholesterol ester deposition in the aortic vessels, an increase in serum low-density lipoproteins **[41],** and an abnormal isozyme pattern of lactate dehydrogenase in aortic tissues, which is a sign of atherosclerotic disease. Along with these atherosclerotic alterations brought on by CO exposure, this pollutant causes tissue B6 deficiency at low levels and alters the vitamin's pattern of urine excretion **[42].**

Biomarkers for Atherosclerosis

The identification of biological markers of atherosclerosis is crucial for preventing the development, progression, and complications of the disease. Algorithms stratifying the cardiovascular risk are useful tools for detecting people who would benefit from primary and secondary prevention. However, some patients at risk fall in the lower categories **[43]**. For this reason, recent studies are focusing on additional screening methods, such as serum, genetic and imaging markers of atherosclerosis, as extensively reviewed Tibaut et al. **[44, 45].** The most widely recognized nonspecific biological marker of inflammation is high-sensitivity C-reactive protein (hsCRP). CRP is a plasma protein synthesized primarily by the liver and, to a lesser extent, by endothelial and atheroma cells **[46]**. It is an acute-phase reactant, released in response to acute inflammatory stimuli, and is considered a risk biomarker for cardiovascular events **[47].** Yousuf et al. **[46]** reviewed CRP involvement in the atherosclerotic process. CRP is considered proatherogenic, acting at early and crucial stages of plaque formation. It binds oxLDL and triggers monocyte-macrophage activation and inhibits eNOS, impairing vasodilation and

promoting endothelial dysfunction. Furthermore, in atherosclerosis, IL-6 produced by foam cells induces the production of small quantities of CRP. For clinical purposes, most trials found the cutting value of hsCRP ≥ 2 mg/l a reliable marker of inflammation and, therefore, a predictor of CV events, although the CRP value for assessing the risk for CVD is limited **[48].**

Arterial wall calcification is a marker of atherosclerosis. A useful tool to assess it is the coronary artery calcium score (CAC) that measures the amount of calcium in the coronary artery wall by means of computed tomography (CT). CAC is a good predictor of CVE and is useful for the stratification of asymptomatic individuals and to detect those who will benefit from early treatment, such as subjects with moderate risk for CVD. The Agatston score is used to measure wall calcium, which is standardized for coronary arteries. However, it is also used for another vascular trees but with great variability **[49].** A CAC = 0 is considered very low risk for CVD whereas that >300-400 defines patients at high risk. Within the context of the Multi-Ethnic Study of Atherosclerosis (MESA), participants were followed during 10 years to evaluate the accuracy of biomarkers to predict CVD. Among the negative risk markers for CVD, a CAC = 0 was the most accurate to reclassify patients into a very low risk group and, therefore, less likely to benefit from preventive pharmacological treatment **[49].** Coronary calcification has better correlation with CVE than other imaging methods, and having calcifications in other vascular beds increases the risk for CVE **[50]**. In this sense, another MESA study demonstrated that multisite atherosclerosis increased the risk for CVD, especially in subjects with risk factors. The authors also found that CAC is the strongest predictor marker for CVD **[51].** Considering the concerns about the risk associated with radiation and the advantages of having an accurate stratification of CVD risk, it is important to establish which subjects will benefit for further explorations. In this regard, latest guidelines recommend CAC as a useful tool to refine risk assessment upward or downward in individuals with predicted risk of 5% to 20% for CVD **[52].**

Treatment

The prevalence of peripheral artery disease (PAD) has grown globally. The indications for treating PAD include a restriction in the amount of pain-free walking distance (intermittent claudication) or tissue ulceration [**53**]. In many arterial locations, endovascular therapy has replaced open surgical surgery as the preferred form of treatment since it is less invasive [**54, 55**]. Treatment of the common femoral artery (CFA) is not yet included in this. In this situation, surgical endarterectomy is still regarded as the "gold standard" of care. The primary 1-year patency rates following surgical endarterectomy are 85–95%, according to the literature [**56**].

Endovascular therapy may be able to replace open surgery, at least for specific structural features of CFA lesions, according to several modest studies [**57**–**60**].

The CFA is recognised as a difficult vessel segment for endovascular therapy because of the probable high stress brought on by its placement in a motion segment. Consequently, surgery has always been used to treat this vascular segment. Although certain trials, particularly the randomised controlled TECCO trial, have recently shown favourable outcomes following endovascular therapy [**61**]. A therapy option for the CFA is stent angioplasty, which has a poor rate of target lesion revascularization (TLR). In most instances, post-procedure problems can be managed conservatively or endovascularly. In order to discover potential lesion characteristics that may benefit from one or the other revascularization strategy, additional comparative studies comparing this endovascular alternative with surgical therapy are required **[62].**

Arteriosclerotic Obstruction treated by LDL

It is well known that the level of low-density lipoprotein (LDL) cholesterol in the blood is closely related to the clinical occurrence of obstructive coronary lesions like angina or myocardial infarction. Serial angiograms have shown that reliable LDL cholesterol removal by an extracorporeal LDL adsorption technique is followed by a regression of the arteriosclerotic lesions **[63].** A relationship between hypercholesterolemia, particularly elevated levels of LDL, and the incidence of ischemic coronary lesions has generally been recognised, as described in the reports of the Framingham study. However, there have not been many descriptions of dyslipidemia, in relation to ASO in the lower extremities, published **[64].** In 33 ASO patients with hypercholesterolemia, a novel therapeutic approach called LDL adsorption was used. Most patients' subjective ASO symptoms improved. The results of the physiologic tests were consistent with and backed up the improvements in subjective complaints. Neither before nor after the LDL adsorption treatments were any major issues or undesirable effects noticed. In treating ASO patients with dyslipidemia, LDL adsorption seems to be a helpful and secure therapy option **[65].**

Transluminal Treatment of Arteriosclerotic Obstruction

Successful use of surgical techniques like endarterectomy, angioplasty, and grafting has largely been limited to highly specialised vascular surgeons, of which there are far too few to deal realistically with the millions of patients experiencing the painful, disabling, or fatal effects of the disease. Additionally, surgical success in treating occlusions in smaller arteries is practically

limited **[66-68].** Consequently, gangrene brought on by femoropopliteal occlusion sometimes necessitates amputation, even though aorto-iliac thromboendarterectomy has typically been successful. If tolerable intermittent claudication is the only handicap that results from low femoral lesions. **[69]** These facts led to the creation of a safe, easy-to-use technique for directly overcoming arteriosclerotic constriction and occlusion in the leg arteries, which was the result of pursuing a previously suggested strategy **[70, 71].**

Transluminal recanalization is a relatively easy procedure. Any physician experienced with vascular catheterization can master the technique; thus, the vascular surgeon's hard-earned expertise is not necessary. A therapeutic approach to arteriosclerotic illness that necessitates the assistance of a skilled vascular surgeon would not begin to scratch the surface of the necessary therapy for a disease that claims a million American lives each year! The cost to the patient is kept to a minimum because the treatment is suited for outpatient application and only occasionally necessitates a brief hospital stay **[72].**

Recent advancement in the treatment

Diet- For people with atherosclerosis, a low-cholesterol, low-fat diet (20–25 grammes per day) has been recommended. Effects of such a diet on patients with atherosclerosis include a decrease in the mortality rate of patients with coronary thrombosis and myocardial infarction following the initial heart attack, a decrease in total serum lipids, neutral fats, chylomicron, and lipomicron counts, as well as an improvement in wellbeing, work capacity, and energy output **[73].**

The following overview describes a low-cholesterol, low-fat diet:

Eat only low-cholesterol foods, such as whole grains and all animal fats. Sparingly use vegetable fats. (Plant sterols such as phytosterol and sitosterol are not significantly absorbed by the gastrointestinal tract, but a high-fat diet appears to increase cholesterol synthesis.) It is advised to take a daily vitamin supplement containing vitamin A concentrate. Soups produced with skimmed milk, vegetable broth, bouillon, and fat-free vegetable soups are all permitted foods. Lean meats, broiled, roasted, baked, or boiled fish and two whole eggs maximum each week; egg whites as required. All whether cooked or raw, but particularly the green and yellow vegetables that are high in vitamin A, such as mustard greens, beetroot greens, chard, spinach, carrots, and kale. All types of fruits, including dried, tinned, and uncooked varieties. Every day, consume tomatoes or citrus. Any type of raw or cooked fruit or

vegetable salad, as well as gelatin salads. Serve with boiled or low-fat dressings, such as those made with refined mineral oil, spices, and vinegar. Beverages included Tea, coffee, or coffee substitutes: tomato juice, fruit, or vegetable juices.

Foods to be avoided:

Cream Soups. All glandular organ meats, including liver, brains, kidneys, and sweetbreads; pig and extremely fatty meats; fat fish; and fish roe. Whole milk, cream, Swiss, cheddar, and all rich cheeses and cheese spreads; excessive butter and milk products. Egg yolks and pancakes, waffles, coffee cakes, muffins, doughnuts, and hot breads Desserts include baked goods, frozen desserts, rich cakes, and cookies that are created with cream and egg yolks. The excessive use of fats in any form, including suet, chicken, or pork fat, vegetable or olive oils, and salad dressings.

Lipotropic Agents- The efficacy of lipotropic drugs in preventing or absorbing atherosclerotic lesions in experimental animals with atherosclerosis has prompted clinical trials and reports in human patients with coronary atherosclerosis. Patients with coronary atherosclerosis have been encouraged to take choline and inositol to lower their death and morbidity rates. A daily average of 6 g of the base has been the dosage for only choline. 4c-inositol alone has been taken on average every day for up to three years at 3 g **[74].**

Endocrine Agents- The thyroid has a long history of influencing lipid and cholesterol metabolism. It has been discovered that thyroid extract, taken in quantities of typically 1 to 3 grains per day, is effective in lowering the hypercholesteremia linked to hypothyroidism. Thyroid extract has been proven to be effective in lowering any associated hypercholesteremia in patients with subnormal basal metabolic rates or subnormal blood iodine levels. For a better metabolic approach to the condition, it is therefore advised to measure the blood iodine level, or basal metabolic rate, in atherosclerotic patients **[75].**

The combination of a low-cholesterol, low-fat diet (20–25 grammes per day), a choline-inositol supplement taken after meals, and, when indicated by clinical and/or laboratory examinations, thyroid and/or oestrogen and androgen hormones has been shown to produce the most satisfactory therapeutic outcomes in atherosclerotic patients.

Torsion of the spermatic cord in the new born

Even though there are not many documented cases of torsion of the spermatic cord in new born, the fact that we have seen two of these cases in the past nine months has thinking that the condition might be more prevalent than the published data suggests. If so, it would suspicion that one prevalent cause of unilateral atrophic testicle, which is frequently seen in urologic practise. Since atrophy or suppurative gangrene may only be prevented by early diagnosis and knowledge that such a condition happens, doctors may become more aware of the issue **[76].**

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