

Atherosclerosis: A Silent Killer

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Cardiovascular disease (CVD) remains the leading cause of death worldwide taking an estimated 17.9 million lives each year (i.e. 32% of all the deaths) [1]. Atherosclerosis, today is one of the major causes of atherosclerotic cardio vascular diseases (ASCVD) leading to severe health problems. Atherosclerosis is the build-up of plaques within the blood vessels that pose a potential risk to the flow of blood leading to increased blood pressure and sometimes causing rupture of arteries contributing to myocardial infarction (commonly termed as stroke). The present scenario is further alarming as atherosclerosis is now a disease of both young and aged, however in recent times reports have documented the increase of atherosclerosis in young adults and women from almost all ethnic backgrounds [2]. Atherosclerosis now is no longer a disease of the Western countries [3]. These trends of spurred disease occurrences have raised questions beyond the known facts of the disease. The primary cause of the disease is hyperlipidemia, specifically the increase in the level of the bad cholesterol or Low density lipoprotein (LDL) cholesterol and a decrease in the level of high density lipoprotein (HDL) cholesterol. High blood pressure and smoking is also a potent cause of atherosclerosis [4]. Beyond the traditional factors causing the disease, research is now focused on newer aspects like the effect of triglyceride rich lipoprotein in the disease progression. Furthermore, the protective role of HDL has become a matter of debate in the recent times. Research is now being shifted to newer challenges such as the association of atherosclerosis with disturbed sleep patterns, stress, sedentary lifestyle, pollution, microbiome, unhealthy diet and environmental stress. The risk of atherosclerosis increases with age and the quality of life in today's world amplifies the risk. Increased obesity, insulin resistance, diabetes and other health complications are all associated with atherosclerosis. Social awareness towards a healthy and fit lifestyle is the choice of today's young adults to keep the risk of atherosclerosis at bay but despite major efforts to reduce ASCVD burden with conventional risk factor control, significant residual risk remains. This review aims to discuss the different risk factors leading to atherosclerosis and the newer perspectives that would inhibit such factors and provide long-term benefit.

Atherosclerosis: Atherosclerosis is a persistent situation of aggregation of plaques within the arteries that obstructs blood flow is causing myocardial infarction in severe cases [5]. Atherosclerosis has been a human disease for more than 3,500 years; that was first witnessed in the Egyptian mummies [6]. Atherosclerosis is the predominant vascular disease worldwide. It is a condition of chronic inflammation. It is a phenomenon that begins in childhood and increases with age. Eventually the presence of associated risk factors aggravates the rate of atherosclerosis. Atherosclerosis often has no symptoms until a plaque ruptures or the build-up is severe enough to block blood flow.

The mechanism of plaque formation: The mechanism of plaque formation is a complex that involves several phenomena. However the primary condition of hyperlipidemia induces the deposition of LDL cholesterol within the blood vessels. The interaction of different processes like inflammatory cell recruitment, foam cell formation, apoptosis and necrosis, smooth muscle cell proliferation, matrix synthesis, calcification, angiogenesis, arterial remodeling, fibrous cap rupture and thrombosis. Each of these plays an important role in plaque formation and is displayed variably in every individual causing unpredictable progression rates. In most cases the plaques occur at the subclinical stage (asymptomatic) and show no signs of the disease. In obstructive condition they cause stable angina and in the acute condition they cause a thrombus and cause myocardial infarction. The complex process of plaque formation can be simplified in five basic steps (7): i) endothelial dysfunction; ii) formation of lipid layer or fatty streak (build-up of LDL) within the intima; iii) oxidation of LDL; iv) migration of monocytes and macrophages uptake of oxidized LDL by macrophage scavenger receptors, and transformation of macrophages into foam cells; v) formation of a fibrous cap to stabilize the plaque. Atherosclerosis is a process of chronic inflammation; hence each step is guided by signature inflammatory cytokines, which could probably serve as a diagnostic marker much early than the conditions get acute.

Risk factors of Atherosclerosis

Unhealthy blood cholesterol levels

Cholesterol, produced within the liver has many functions from building cells to nerve insulation. But cholesterol also enters our body from food, such as animal-based foods like milk, eggs, and meat. Too much cholesterol in the body is a risk factor for development of heart disease [9]. The cholesterol builds up in the walls of the arteries, by atherosclerosis and narrows the lumen of the arteries which poses an obstruction to the blood flowing to the muscles of the heart. As a result due to improper and insufficient blood supply angina or chest pain is experienced. In conditions when there is a complete obstruction of the arteries there is a complete blood supply cut-off and a myocardial infarction is caused. There are two forms of cholesterol that many people are familiar with: Low-density lipoprotein (LDL or "bad" cholesterol) and high-density lipoprotein (HDL or "good" cholesterol.) These are the forms in which cholesterol travels in the blood. LDL is the main source of plaque forming in the arteries. The HDL protects against heart disease and has a potent role in solubilizing the plaques. The following affecting the cholesterol levels are as follows:

- **Diet:** Saturated fat, trans fat, carbohydrates, and cholesterol in the food increases cholesterol levels. Lowering the levels of saturated fats, trans fats and sugars directly reduces the total cholesterol of the blood which is a major requisite to prevent atherosclerosis. Fiber and sterols help to decrease the level of LDL cholesterol.
- **Obesity:** In addition to being a risk factor for heart disease, being overweight can also increase the cholesterol levels. Losing weight helps to lower the LDL, total cholesterol levels, and triglyceride levels, as well as raise your HDL [10].
- **Exercise:** Active lifestyle and regular exercise of at least 30 minutes a day can lower LDL cholesterol and raise HDL cholesterol.
- **Age and Gender:** Studies have documented that the females are protected from heart diseases at least for a decade more as compared to males because before menopause, women tend to have lower total cholesterol levels than men of the same age. This condition gets reversed after menopause and the level of LDL shows a steady increase in women. Hence, age and sex influences the level of cholesterol.
- **Heredity:** Genetic inheritances partly determine how much cholesterol your body makes.
- **Medical conditions:** Occasionally, a medical condition like hypothyroidism may cause an elevation of cholesterol levels in the blood.
- **Medications:** Steroids and progestins, may increase "bad" cholesterol and decrease the "good" cholesterol.

Increased plasma levels of blood Triglycerides has been associated with atherosclerosis even if low-density lipoprotein cholesterol levels are at goal but the exact mechanism of its pro-atherogenesis is still not clearly documented.

High Blood Pressure: Innumerable studies strongly indicate that hypertension is a major cause of different pathological conditions of heart diseases ranging from mild atherosclerosis to obstructive fatal condition due to sudden insufficiency causing death [11]. The mechanical stress exerted on the blood vessels as a result of hypertension has severe consequences on the cardio vascular system. The deleterious effect of the elevated blood pressure on the cardiovascular system appears to be due mainly to the mechanical stress placed on the heart and blood vessels. High blood pressure often does not show any severe symptoms and gets undiagnosed which causes a risk factor for atherosclerosis. Only 35% of the people have blood pressure under control. High blood pressure causes the blood to pass forcefully through the arteries which causes strain and stress, as result of which the thin delicate inner endothelial lining of the arteries gets injured and becomes stiff over time. Such a kind of a lining serves as a route for entry of more leucocytes and LDL cholesterol to enter the endothelial wall and gets deposited as a plaque on the walls. Gradually with uncontrolled hypertension, the plaque increases and in severe conditions might cause obstruction of blood flow leading to myocardial infarction which is often fatal.

Smoking: Smoking is one of the major causes precipitating Atherosclerosis in a complex manner. Smoking lowers the "good cholesterol" or HDL and increases the "bad cholesterol" or LDL. Smoking serves as a source of Nicotine and carbon monoxide which induces changes in the endothelium and aggravates plaque formation [12]. Although smoking does not cause hypertension directly but due to the narrowing of the arteries, the blood flow faces obstruction. Studies have also documented that smoking indirectly causes hypertension by stimulating the nervous system. Studies have documented that smoking increases inflammation, thrombosis and oxidation of low-density lipoprotein cholesterol and prepares the arterial intima for atherosclerosis. An increased inflammatory response is observed at the onset of atherosclerosis. Smoking stimulates the production of pro-inflammatory cytokines, which also helps in the migration of

leucocytes within the arteries leading to atherosclerosis. Reports have shown the increased presence of different adhesion molecules like VCAM-1, ICAM-1 in smokers that promote leucocyte recruitment.

Insulin resistance, obesity or diabetes: Insulin resistance and diabetes is one of the major causes of atherosclerosis which complicates the disease furthermore. Insulin is the hormone that controls the concentration of blood sugar, whereas insulin resistance poses a hindrance to this process causing diabetes [13]. Subjects with diabetes have a predominance of cardiovascular diseases, atherosclerosis and myocardial infarction as compared to non-diabetic individuals with same risk profile. Hypertension, dislipidemia, glucose intolerance and obesity under the influence of different genetic and environmental factors cause insulin resistance phenotype also referred to as a metabolic syndrome. Such a condition aggravates atherosclerosis. Obesity is the most common nutritional disorder that has increased in recent times in young adults due to sedentary lifestyle and food habits. A low HDL-cholesterol is the hallmark of obesity which causes atherosclerosis progression. Studies have corroborated that adipose tissue involved in energy storage plays a role in metabolic processes like hormone secretion and efflux of cholesterol. Obesity is one of the major risk factors for the development of both impaired glucose tolerance (or prediabetes) and type 2 diabetes and its prevalence worldwide drives toward an increased rate of cardiovascular morbidity and mortality. Thus the cross talk between the mechanisms of obesity, insulin resistance is thus an important facet for development of atherosclerosis.

Sleep Apnea: Sleep apnea is a severe disorder in which breathing repeatedly stops and starts during sleep and causes fragmented sleeping patterns [14]. This disorder is commonly seen in men and is often aggravated with obesity and age. The condition poses a serious threat as during conditions of momentary cessation of breath hypoxia results which can be fatal. Although the mechanism of obstructive sleep apnea cannot be directly correlated with atherosclerosis but studies have shown that subjects with metabolic disorder are more prone to it. Studies have shown a reduction in hypertension and triglyceride in subjects of a randomized trial after treatment with continuous positive airway pressure. Furthermore, studies have consistently shown that obstructive atherosclerosis was associated with increased cardiovascular mortality independent obesity. Taken together, these results support the concept that obstructive sleep apnea exacerbates the cardiometabolic risk attributed to obesity and the metabolic syndrome. Recognition and treatment of sleep apnea may decrease the cardiovascular risk in obese patients. Such can be successfully achieved by following a healthy lifestyle pattern.

Lack of exercise: Studies have shown a decreased incidence of cardiovascular disease in individuals having an active lifestyle with adequate physical activity [15]. The individuals with lack of physical activity have twice the risk of atherosclerosis leading to cardiovascular diseases. Exercise can improve endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels in patients with chronic heart disease. It also improves both basal endothelial NO production and agonist mediated endothelium-dependent vasodilatation of the skeletal muscle vasculature in patients with congestive heart failure. Additionally, a single session of moderate intensity exercise documented improved endothelial function and attenuates the effect of ingestion of high fat meal in lean and obese subjects. There are innumerable reports which documented a reduced risk of developing atherosclerosis and CVD in individuals with regular physical activity and exercise. However, the exact mechanism of physical activity influencing the lipoprotein metabolism and endothelial function is still to be elucidated.

Family History and Atherosclerosis: Research has shown that the risk of developing atherosclerosis can be influenced by heredity [16]. However, researchers have been unable to identify the specific genes associated with this risk clearly. Family history of atherosclerosis has been acknowledged as a significant cardiovascular risk factor. Lipid levels, together with hypertension and diabetes, are all associated with the genetic constitution of a family and is very much a heritable component. Reports have documented that patients with a family history of atherosclerosis have a higher prevalence of VLDL triglyceride/HDL cholesterol ratio above 1.8 than patients without.

Healthy lifestyle changes to combat atherosclerosis: Lifestyle modifications have served as boon towards reducing the risk of atherosclerosis [17]. A healthy diet, regular exercise, normal undisturbed sleep patterns essentially reduces the risk of atherosclerosis. Some of the healthy lifestyle changes recommended are as follows:

- Quitting smoking
- Eating healthy foods
- Exercising regularly
- Maintaining a healthy weight

- Checking and maintaining a healthy blood pressure
- Checking and maintaining healthy cholesterol and blood sugar levels

Conclusion: Atherosclerosis is steadily increasing in the modern world and the disease has no barriers. In spite of being a non-communicable disease it is one of the most fast progressing diseases because of the lifestyle that we have adopted. Simple lifestyle changes can cause a marked difference in slowing the disease pathogenesis. It is now known that hyperlipidemia, obesity, insulin resistance due to metabolic syndrome have a positive association with atherosclerosis. Oxidative changes and phases of increased inflammation have been observed in atherosclerosis, hence several antioxidants and agents suppressing inflammation are used additionally along with the mainstay therapy. Awareness among the masses and a little orientation regarding the disease can really make a difference.

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