Atherosclerosis: Causes and Cures

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Research Article

Abstract
Atherosclerosis is a systemic disease that occurs due to the formation of fibro-fatty lesions in arteries that block blood flow. The process of Atherosclerosis is initiated through mechanical, chemical, and immunological activation of the endothelium. Even there are microorganisms involved in the different stages of atherosclerosis. There are a number of molecular factors, RNA’s, macrophages, and enzymes that play a vital role in the progression and development of Atherosclerosis that alter the metabolism of fibro-fatty. Receptors of micro RNA proliferate and regulate endothelial activation and smooth cell Macrophages, monocytes, t-cell, and natural killer cells are involved in the boosting of the immune system to prevent atherosclerotic lesion formation. In this review, we can know how RNA’s involved in the pathophysiology side of atherosclerosis and explore the mechanism to regulate Atherosclerosis, and how macrophages evoke an immune response. Therefore, the use of synthetic and natural drugs and following the right diet timely prevent and reduce the risk of development of Atherosclerosis.

Keywords: Atherosclerosis, Fibro-fatty, RNA, Cardiac vascular disease

1. Introduction
Cardiac vascular disease (CVD) is one of the leading diseases that affect the whole world. CVD includes Ischemic heart disease, Myocardial-infarction, and Atherosclerosis. CVD is the leading cause of death in India, when compared with a western population only 23% of people below the age of 70 are affected by CVD whereas in India above 52% of people are affected due to an imbalanced diet, use of Tobacco, alcohol intake and smoking. Atherosclerosis is the vital cause of death in industrialized societies, soon to be worldwide. Atherosclerosis is a systemic disease that affects elderly people. It is the hardening and narrowing of arteries. Arteries are responsible for the flow of oxygen-rich blood from the heart to the entire body at a young age but as we grow older our arteries become narrow and harden and there is a formation of fibro-fatty lesions in arteries that may block the flow of blood. It changes the accumulation of lipids, calcium, blood components, carbohydrates, and fibrous tissue on the intimal layer of the artery.
The recent update found that the intracellular bacterial pathogen *Chlamydia pneumoniae* causes respiratory tract infection and has been associated with atherosclerosis and coronary artery disease. *C. pneumoniae* is involved in all stages of atherosclerosis including initiation, inflammation, fibrous plaque formation, plaque rupture, and thrombosis (James and Brian, 2001). A low level of ascorbic acid is a major risk factor and indicator of atherosclerotic CVD, including hypertension and elevated concentrations of LDL, acute phase proteins, and hemostatic factors (Sagar et al., 2012). Increased platelet action in the body can increase the atherosclerosis risk and plaque calcification also increases the risk of atherosclerosis (Amala et al., 2012). Leptin may contribute to the development of classic risk factors of atherosclerosis such as arterial hypertension and diabetes mellitus (Jerzy, 2006).

As we are living in a modern and technological world we have no time to get good sleep and we are in a hurry and get pressure at work so that we get stress and depression because that we may also have a chance of getting atherosclerosis. We may prevent it by doing yoga, listening to music, and gardening.

2. **Molecular and Cellular of Atherosclerosis**

Atherosclerotic vascular disease is the cause of Myocardial-infarction, stroke and ischemic heart pain, and sudden cardiac death. These diseases are the leading causes of death in the world, as a result, it also causes obesity and type 2 Diabetes which are potent risk factors of atherosclerosis. This disease is initiated by subendothelial retention of apolipoprotein B (apoB) –containing lipoproteins in the focal areas of arteries. (Ira Tabas et al-2015). About 462 genes have been manipulated by molecular methods to study their effects on the initiation, promotion, and progression of atherosclerosis. There are signaling pathways that are highly relevant to atherogenesis, these pathways include insulin receptors; Ras and MAPK activation; above 75% of alternate transcriptional start sites, and alternate splice sites are found in human genes, they provide isoforms with the flexibility of expression. From cancer literature, they adapted four major steps that manifest atherosclerosis. The steps are 1) initiation of endothelial activation and inflammation; 2) promotion of intimal lipoprotein deposition; 3) progression of complex plaques by plaque growth, fibrosis, thrombosis, and enlargement of necrotic core,4) precipitation of acute events like myocardial infarction, sudden coronary death.

The chemical, mechanical or immunological insult or injury or activation of endothelium leads to endothelium dysfunction which initiates the atherosclerosis process. Endothelium dysfunction also triggers the inflammatory response. Macrophages, monocytes, vascular smooth muscle cells, T-lymphocytes are involved in the inflammatory response.
The progression and complication of molecular determinants of atherosclerosis are numerous. Elevated plasma lipids and glucose are the major molecular risk factors of atherosclerosis and cardiovascular disease. Hypertension, smoking, and aging are non-molecular risk factors but when they undergo molecular action of intermediates of inflammation oxygen balance they may be a major contribution of atherosclerosis.

Retention of lipoprotein is the key initiation of atherosclerosis and increases the level of plasma lipids particularly low density and very-low-density lipoprotein induces dysfunction of the endothelium. In atherosclerosis progression and complication, molecular factors like growth factors, chemokines, enzymes, and vasoactive substances, and apoptosis signals are involved. These molecular factors are involved both as a marker for atherosclerosis disease and play an important role in the pathogenesis of the disease. Inflammatory cells that present in atherosclerotic lesions at the development stage exhibit markers prominent in sites of plaque rupture. (E. Mannarino, et al-2008). The development of molecular pathways involved in lesion progression and the mechanism in atherosclerotic plaque are understandable for the last several decades.

3. Role of RNA in atherosclerosis

MicroRNAs (miRNAs) are defined as single-standard, non-coding RNA molecules that synthesize protein by interacting with messenger RNAs (mRNA). MicroRNA is also used for its role in tempering gene expression. The gene expression is suppressed by miRNA either by cleaving or degrading its target mRNA or inhibiting the translation process. In a report, they say that miRNA plays an important role in silencing target genes and also reduces the synthesis of protein and function of cells, therefore it has been substantiated that miRNA plays a vital role in endothelial injury, cell attachment, growth, and inflammatory responses. It also suggested that miRNA act as a regulator of smooth muscle proliferation and phenotypic changes and also influence macrophage activity. Thus by understanding this influence, Yao Lu et al said that miRNAs present on these cells drive the progression of atherosclerosis and its role in the process of vascular disease.

Figure 2: Role of RNA in atherosclerosis
(Yao Lu-2018)

MiR -34a, miR217, and miR-146a are types of microRNA. MiR -34a influences proliferation and differentiation in endothelial cells, overexpression of miR34a in endothelial cells decreases Sirtuin-1[SIRT-1] levels. Various studies say that an increased level of miR34a in atherosclerotic arteries is due to miRNA.
MiR-22 was transcriptionally regulated by the action of TGF-β1, involving a p53-dependent mechanism. MicroRNAs responsible for regulating SMC differentiation—MiR-143 and MiR-145—are decreased in diseased vessels. This suggests that a reduction in the expression of these microRNAs shows the differentiation of SMCs that influence the formation of the lesion that is responsible for the progression of atherosclerosis.

MiR-1 was observed to steadily increase in the differentiation process from embryonic stem cells to SMC. MiR-1 induces SMC differentiation by the repression of Klf and Pim-1 (a serine/threonine kinase) which serves as a negative regulator of SMC differentiation. When MiR-10a was increased, Retinoic acid induces SMC differentiation from embryonic stem cells. This increase results from a retinoic acid-induced nuclear translocation of NF-κB. MiR-10a binds to 3'-UTR of HDAC4 which is a negative regulator of SMC differentiation. MiR-21 In a report it says that when MiR-21 is involved in TGFβ- and BMP4-induced SMC differentiation by down-regulating programmed cell death 4 (PDCD4), which is a repressor of SMC contractile genes. However, there was still evidence that MiR-21 is repressed by the increase.

Non-coding RNAs play a key role in gene transcription, post-transcriptional processing, chromatin modification, and epigenetic changes. Especially IncRNAs play a vital role in the growing number of human systemic diseases such as cardiovascular, cancer, and immune diseases. The initiation, propagation, and development of atherosclerosis, obesity-associated systemic inflammation, and oxidative stress play an important role.

4. Immunological aspects
The immune response was transported by the induction of monocyte-derived cells into subendothelial space, which differentiates into mononuclear phagocytes that process accumulated normal and modified lipoproteins, and change them into cholesterol-laden "foam cells". Foam cells are classified as a 1) type of macrophage, 2) persist in plaques, and 3) promoting disease progression. Macrophages are the most important immune cell in arterial plaques, have been evoked to play a vital role in immune responses and progression of atherosclerosis. Macrophages primarily initiate from circulating monocytes and resident tissues. They are employed to the lesion site by holding to activated endothelial cells (ECs) and move into the sub-endothelial cell space. Then, macrophage proliferation enhances the major replenishment mechanism in plaques. Macrophages are the essential cells in atherosclerosis, with the quantity and phenotype of cells in plaques inducing both disease progression and regression. (Kathryn Moore et al-2013).

Studies have shown that increased lesion CD68+ macrophages are linked with a complex risk of CVD and stroke. Macrophages are heterogeneous and are categorized into pro-inflammatory and anti-inflammatory phenotypes, which are known as M1 and M2 phenotypes. (Sozzani S, et al-2004).

Atherosclerosis is a non-resolving inflammatory condition, in which monocytes continue to enter plaques and differentiate into macrophages as atherosclerotic lesions progress. Significantly, macrophages promote size-independent changes in plaque morphology, remarkably necrotic core formation, and fibrous cap thinning that describe vulnerable plaque. The methods of these processes in plaque progression are predominantly relevant to acute atherothrombotic cardiovascular disease in humans. (Virmani et al., 2002).
Although monocytes are active in the plaque during the growth, they have the potency to emigrate from the plaque, under some experimental conditions that are related to a decrease in plaque size and regression of atherosclerosis. Monocytes may enter lymphatic vessels and move to drain lymph nodes, or they may migrate across the arterial endothelium to the artery lumen and directly enter the circulating bloodstream.

5. Drugs
Cholesteryl ester transfer protein (CETP) is a lipid transfer protein that enables the transport of cholesterol ester and TG inside the lipoproteins in the blood to resolve the method of transfer of cholesterol ester from the HDL to the LDL and VLDL which have to be proatherogenic. Therefore the movement of cholesterol esters from HDL to LDL by CETP starts lowering HDL. Inhibition of CETP is a choice of treatment in the lipid profile associated with disorders like atherosclerosis and type II diabetes.

5.1. Synthetic drugs
In many classes, cardiovascular drugs have established anti-inflammatory properties in their targeted actions on altering the contributory risk factors such as hypertension and hyperlipidemia. Among the antihypertensive drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to inhibit the inflammatory effects of angiotensin II within the modulation of pro-inflammatory cytokines, NF-kB, oxidative stress, and nitric oxide synthesis. Over 50 000 000 people in the United States take aspirin for the prevention of coronary heart disease and due to clear benefits that exert on the risk of clinical outcomes by the reduction of platelet activation and aggregation mainly by inhibiting platelet COX-1.
5.2. Vaccines
The effect of immunization with LDL was thought to result from the antibody-mediated elimination of oxidized LDL particles, but studies suggested that antigen-specific TREG is an essential anti-inflammatory mechanism. An LDL vaccine against atherosclerosis is under development and expected to be evaluated in clinical trials in the future.
(GK Hansson et al., 2015)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Animal model</th>
<th>Effects of surrogate markers and disease epidemiology</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>Folic acid antagonist</td>
<td>↓ Atherosclerosis and intima-media ratio in hypercholesterolaemic rabbits</td>
<td>↓ Myocardial infarction</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Microtubule inhibition</td>
<td>↓ Atherosclerosis in hypercholesterolaemic rabbits</td>
<td>↓ Myocardial infarction</td>
<td>↓ Cardiovascular disease</td>
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<tr>
<td>Canakinumab</td>
<td>IL-1β neutralizing monoclonal antibody</td>
<td>NA</td>
<td>↓ Levels of CRP and other inflammatory markers</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Ustekinumab, briakinumab</td>
<td>Monoclonal antibodies against the IL-12 subunit p40 (common to IL-12 and IL-23)</td>
<td>↑ Atherosclerosis after IL-12 administration to Apoe−/− mice ↓ atherosclerosis in Apoe and Il12 double-knockout mice</td>
<td>↔ Cardiovascular risk ↑ cardiovascular risk</td>
<td>NA</td>
</tr>
</tbody>
</table>

(↑-increase; ↓- decrease; ↔-no change occurred; NA-non available)
(GK Hansson et al., 2015)

5.3. Natural drugs
The medicinal properties of garlic (Allium sativum L.) are known for thousands of years. The valuable effects of garlic in the treatment of cardiovascular diseases (CVD) were tough to prove because of the mild effect, long frame, and complex pathogenesis of atherosclerosis and related CVD. Garlic-based preparations are supposed to have cardioprotective and anti-atherosclerotic effects, such as improving blood lipid profile, inhibiting cholesterol biosynthesis, suppressing low-density lipoprotein (LDL) oxidation, modulating blood pressure, controlling platelet aggregation, lowering plasma fibrinogen level, and increasing fibrinolytic activity. These potential effects appear to be very promising to the extent of challenge for atherosclerosis on modern medicine and essential for novel and safe medications. Atherosclerosis is a multifactorial disease, which is not entirely dependent on conventional cardiovascular risk factors. Direct anti-atherosclerotic effects of garlic therapy in atherosclerosis should prevent the growth of prevailing atherosclerotic lesions and the formation of new ones. The most intriguing property of garlic-based preparations is direct anti-atherosclerotic activity, which is independent of the moderate reduction of cardiovascular risk factors associated with garlic. The components in garlic can control two important intracellular enzymes that are responsible for cholesterol intracellular metabolism. Allicor, a garlic-based preparation, prevented cholesterol accumulation in cultured cells when treated with serum from atherosclerosis patients after a single dose, this was shown to reduce serum atherogenic potential. Garlic ingredients are known to inhibit inflammation signaling,
including TNF, IL-1-beta, ICAM-1, and HLA-DR expression and secretion. Therefore, they have beneficial effects at the arterial wall cells level. (Sobenin et al., 2019)

Figure 4 - Plausible effects of medicinal plants on different stages of atherosclerosis development
(Tatiana V kirichenko et al., 2020)

Use of pomegranate (Punica granatum L.), which has multiple anti-atherosclerotic activities. Thus, ellagic acid that is present in the pomegranate promotes cholesterol deletion by regulating the LXR/PPAR-ABCA1 pathway. Pomegranate peels up-regulate mRNA expression of LXRα and ABCA1. ROS levels produced by mitochondria are reduced by ellagic acid and punicalagin in pomegranate by an antioxidant effect. Moreover, pomegranate possesses an anti-inflammatory effect due to pomegranate peel, flower, and seed oil that may reduce plasma levels of IL-6 and TNFa, pomegranate flower increases the anti-inflammatory cytokine IL-10 and, in addition, pomegranate extract reduces the translocation of NF-κB from the cytosol to the nucleus. LPS-induced pro-inflammatory cytokine activation is decreased by Pomegranate ellagic acid, peel polyphenols, and punicalagin.

6. Spices
Nutrition research recommended that the nutrients contained in vegetables and fruits offer a host of athero-protective effects. For example, the intake of fiber, a plant-based nutrient that is associated with reduced CVD risk. The types of spices consumed vary across cultures (table 3). In the Mediterranean diet, they use herbs and spices commonly in cooking because it increases the
flavor of food and reduces the need for salt and oil. Five-spice powder is a popular condiment in China, and it also includes peppercorns, fennel, cloves, star anise, and cinnamon, all of these spices are proven to improve CVD symptoms.

<table>
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<th>Table 3 - Types of spices consumed across cultures</th>
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<td><strong>Diet category</strong></td>
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<td>---------------------------------------------</td>
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<tr>
<td>Western diet</td>
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<tr>
<td>Mediterranean diet</td>
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<td>Chinese diet</td>
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<td>Indian diet</td>
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<td>Arabian diet</td>
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Studies have shown that the Mediterranean diet (MedD) is associated with a reduction in a variety of inflammatory molecules implicated in atherosclerosis and CVD incidence and mortality as well as an improvement in endothelial functions. The diet’s chief component, extra virgin olive oil (EVOO), contains various bioactive phenolic compounds that possess anti-inflammatory and antioxidative properties. The use of EVOO as the prevention of frequent complications of CVD such as Heart failure and atrial fibrillation.

7. Counseling for Atherosclerosis
Changing risk factors outlines an aging population, the burden of disease is expected to increase. Peripheral arterial disease (PAD) is a global health issue associated with high levels of mortality and morbidity. The prevalence of asymptomatic PAD that is estimated is between 3% and 10% in the adult population. With altering risk factor profiles and aging demographics, this disease burden is expected to increase significantly during the next 20 years. There are local complications of PAD, such as intermittent claudication, loss of function, ulceration, and gangrene, and amputation. It is also an essential marker for systemic atherosclerosis which involves the coronary, cerebral, and renal vascular territories. Individuals with PAD have a two to six times greater risk of cardiovascular and cerebrovascular events compared with age-matched individuals in the general population. Only 20% to 30% of patients with PAD die of non-cardiovascular causes. Therefore, medical and lifestyle management of PAD has to include therapies that improve functional consequences and reduce adverse cardiovascular and limb events. Evidence for these treatments and makes clinical recommendations accordingly. Exercise therapy and regular physical activity are positive predictive indicators for all-cause mortality in patients with PAD. Hence, exercise is the most effective non-invasive therapy to improve pain symptoms and ambulation in intermittent claudication. (Parvar. S et al., 2018)

8. Medication Therapy and Secondary Prevention of CVD
CVD may place individuals at risk for reduced quality of life, heart failure, and death, making secondary prevention crucial. The rate of progression of atherosclerosis is influenced by
cardiovascular risk factors: tobacco use, an unhealthy diet, and physical inactivity (result in obesity) elevated blood pressure (hypertension), abnormal blood lipids (dyslipidemia), and elevated blood glucose (diabetes). For the prevention of cardiovascular disease, it is divided into three steps: primary, secondary and tertiary prevention of arbitrary.

The determination of applying the guidelines is to motivate and assist high-risk individuals to lower their cardiovascular risk by:
- Stop use of tobacco, or reduce the amount smoked;
- Prefer healthy food diet;
- Reducing body mass index (to less than 25 kg/m2) and waist-hip ratio (to less than 0.8 in women and 0.9 in men (these may be different for different ethnic groups);
- Lowering blood pressure (to less than 140/90 mmHg);
- Lowering blood cholesterol (to less than 5 mMol/l or 190 mg/dl);
- Lowering LDL-cholesterol (to less than 3.0 mMol/l or 115 mg/dl);
- Controlling glycemia, especially in those with impaired fasting glycemia and impaired glucose tolerance or diabetes;
- Aspirin (75 mg daily), should be taken once the blood pressure has been controlled.
- Decrease the energy intake and should maintain an appropriate body weight
- Reduce the percentage of energy derived from fat, limit the number of SFAs with polyunsaturated fatty acids (PUFAs), and reduce the intake of trans fatty acids
- Intake of omega-3 PUFAs should be increased

9. Conclusion

The atherosclerosis lesion shows highly specific cellular and molecular responses and the process of vascular injury causes cardiovascular risk and activation of inflammation lesions and apoptosis and the contribution of progenitor cells that repair molecular signals. Micro RNA, non-coding RNA plays an important role in atherosclerosis. The RNAs modulate the pathophysiology of atherosclerosis development. Receptors of microRNA proliferate and regulate endothelial activation and smooth cell Macrophages, monocytes, T-Cell, and natural killer cells are involved in the boosting of the immune system to prevent atherosclerosis lesion formation. The use of natural drugs prevents atherosclerosis without any side effects.

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

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