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Atherosclerosis: Risk factors and emerging role of biomarkers in pathogenesis of atherosclerosis

Naomi Andrew Mbwambo[1], Vandna Kalsi[2], Barinderjit Kaur[1*]

[1]*Department of Pharmacology, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*
[2]*Department of Pharmacognosy, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*

Address for correspondence:
Ms.BarinderjitKaur,

Department of Pharmacology,
School of Pharmaceutical Sciences,
Lovely Professional University, Phagwara,
Punjab, India.
Contact No. 9646133008
email: barinderjit.12062@lpu.co.in

ABSTRACT

Atherosclerosis has been a paramount source of morbidities and mortalities globally. Atherosclerosis is a disease characterized by deposition of lipids and other fatty materials in intima of arteries resulting into narrowing and hardening of arteries. Furthermore, atherosclerosis leads to development of several cardiovascular complications, therefore, identification of associated biomarkers is of great importance.This review focuses on the vital role played by several risk factors and biomarkers in pathogenesis of atherosclerosis.

Introduction

Atherosclerosis is a term obtained from Greek origin, meaning accumulation of fat and thickening of the arterial endothelium [1]. The term, atherosclerosis comprises two words; "athere"- groats, meaning fat deposition accompanied by some macrophages and "sclerosis"- hardening, meaning arterial fibrosis layer becomes hard due to plaque formation, consists of cholesterol, fat, calcium and some other substances present in blood [2]. Due to plaques development, central core becomes accommodated with fatty material [3].

Atherosclerosis is the main cause of other cardio-vascular diseases such as stroke, hypertension, angina and heart attack. Frequently patients realize that they are atherosclerotic when they are

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associated with such diseases.[4] However, symptoms depend on the severity and affected artery or organ [2,3].

Formation of atheromatous plaques within the intimal layers of arteries begins due to accumulation of fat and small cholesterol molecules and its underlying smooth muscle. As the plaques or atheroma formation becomes more prominent, fibrous tissues and the surrounding smooth muscle proliferate, therefore, a bulge formed upon the endothelium causing narrowing of blood vessels and consequently obstructs the blood flow [4]. Further, hardening of the arteries (sclerosis) becomes the cause of connective tissue production due to fibroblasts as well as calcium deposit in the lesion, results into irregular arterial intima that leads to clot formation and/or thrombosis, lastly, sudden obstruction to blood flow occurs [5].

Increase in oxidative damage due to hyperlipidemia and hyperglycemia have always have been affecting lipoprotein levels and antioxidants [6]. Therefore, managing blood lipid levels by lipid lowering drugs and life style changes have been proven to be effective by several studies. Thus, vascular endothelium damage and atherosclerosis can be prevented [6,12].

Epidemiology

Atherosclerosis is a prevalent cause of death globally after other cardiovascular diseases. Now-a-days, this disease is very common as more than 40 million cases occurring annuallyin India [6]. In 2010, nearly 42 million people were suffered from coronary artery diseases as per WHO, therefore, it contributes to one fifth of deaths per year. Moreover, it is estimated that at the end of year2022, it will account one third of all mortalities [7,8].

Pathogenesis

It is crucial to consider the functioning and morphological characteristics of a normal artery as well as to understand the pathology of arteries. The arterial homeostasis depends on the condition of the arterial wall as followed.

The layers of arterial vessel

Normally, three layers constitute the arterial vessels, namely tunica adventitia, tunica media and tunica intima.

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The most interior layer near to the artery lumen is tunica intima, also called endothelium. The endothelium plays a fundamental role in atherosclerosis as lymphocytes, macrophages as well as some of pro- inflammatory mediators mayinfrequentlypenetrate in the intimal lining [9].

The middle layer is tunica media, made up of elasticlaminae that form internal and external borders [10]. This middle layer consists of smooth muscle cells having contractile function (allowing vasoconstriction and vasodilatation),therefore, responsible for the tensile strength of the blood vessel during constriction and dilatation and some other functions including proliferation of the vascular extracellular matrix [9,10].

The last layer of arteries is called tunica adventitia consisting of fibroblasts, other connective tissue, nerves and lymph vessels. Inflammatory mediators during atherosclerosis may also intermittently migrate to adventitia layer [12].

The atherosclerotic cellular components

The various cellular constituentsof endothelial cells and vascular smooth muscle cells in intimal layer and extracellular matrix of the arterial wall are in a regular active interchange. Therefore, afterknowing the physiology of these component'sactive interchange, the functioning of every intimal cellular component and the dysfunctioning due inflammatory mediators leading to atherogenesis can be better understood [13].

Endothelial cells

Endothelial cells in the intimal layer of arteries are involved in homeostasis of intima structurally, metabolically, as well asby signaling functions [14]. The endothelium has several important roles in vascular biology such as follows;

i) Acts as an active and main biologic mediator between the blood and other cells, thereby regulating nutrient and cellular trafficking [15].
ii) Maintains an initialequilibrium between coagulating and anticoagulating activity, inflammatory and anti-inflammatory effects, and contraction and dilatation vasomotor tone [13,15].
iii) Endothelium can also give rise to several prothrombotic molecules after it encounters different stressors, however, it also involved in maintenance of balanced

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anticoagulant state. Moreover, production of antithrombotic molecules by endothelial cells also prevents the blood from clotting [16].

iv) In the regulation of the immune response, endothelial cells responds to local injury or infection by secreting chemokines that have the capacity to attract various leukocytes to the injured area [17]. Along with this, endothelium also produces several adhesion molecules, which attracting more mononuclear cells, after these accumulatein injured site of endothelium layer and, therefore, promote further development of atherosclerosis [18].

v) Furthermore, endothelial cells also release mediatorssuch as vasodilators (prostacyclin and nitric oxide),therefore cause relaxation of SMC in the tunica media as well as vasoconstrictors (e.g. endothelin), thereby modifying their functions [19].

Vascular smooth muscle cells (VSMC)

VSMC play vital role in the pathogenesis of atherosclerotic plaques due to its contractile and synthetic functions, as its contractile functions prevents the intimal wall from weakening that is the major issue of atherosclerosis [20]. For example, aneurysm that occur due to weak intimal lining is a serious complication of atherosclerosis [21].

The synthetic functionsof smooth muscle cells contributes to synthesis of certain fibres including elastin, collagen and proteoglycans. These have been involved in the formation of connective tissue matrix of the arterial wall [22]. Moreover, smooth muscle cells ale also involved in the synthesis of certain inflammatory mediators such as IL-6 and TNF- α. It has been found that these synthetic functions play a dominant role during the atherosclerotic plaque [23].

Extracellular matrix (ECM)

As mentioned earlier, vascular ECM in the tunica media layer made up of collagen and elastin proteoglycans, and these are predominantly generated by smooth muscle cells.[12] With the provision of flexibility and strength due to both these components, the structural integrity of intimal wall is maintained despite high pressure within the lumen[22,24].

The atherosclerosis process

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Atherosclerosis process involves three main processes namely

I. Initiation: Formation of fatty streaks

II. Adaption: Atheroma formation (plaque progression)

III. Clinical complication of atherosclerosis: Atheroma/ plaques formation (plaque disruption)

Formation of fatty streaks

The initial sign of atherosclerosis is proven to be the fatty streaks by various studies conducted in animals and humans. Increase in the proportion of lipoproteins in the intimal lining is usually the cause of initial lesions [25]. Lipoproteins are collectively made up of triglycerides, phospholipids and various proteins, all are crucial atherogenic proteins, causing intimal dysfunction by plaque formation [26].

Plaques normally increase in size from the opposite direction of the blood vessel at the initial steps of atheroma formation. Atherosclerotic blood vessels are known to be growth in diameter, when the internal elastic layer of arteries is covered by more than 40% with plaque. As a result blood flow reduced at the last stage of plaque. Studies have proven that intimal damage with cellular constitents that involves monocytes, smooth muscle cells, and lymphocytes results in atherosclerosis. Furthermore, foam cells, EC fat deposits and few platelets produce the initial soft lesions [27]. As the process progresses, proliferation of smooth muscle cells takes place in the final stages, this intensifies blood into the atheroma/ plaque [27,28].

Four stages occur during the formation of fatty streaks:

i. Low density lipoprotein (LDL) trapping

ii. Endothelial dysfunction (endothelial cells activation)

iii. Leukocytes activation

iv. Generation of foam cells

Low density lipoprotein (LDL) trapping

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Circulating low-density lipoproteins cross endothelial barrier due to endothelial dysfunction, therefore, cause disruption of integrity of intimal wall [29]. LDL particles start to accumulate by binding to proteoglycans. This accumulation leads to atherogenesis as LDL may undergo a number of chemical modifications while retained in the intima for longer time [30]. Hypertension has been known to be involved in progression of atherosclerosis as it increase vessel wall stress, more proteoglycans accumulation in the intimal layer, and thereby encouraging LDL-binding with proteoglycans within intima and contribute to "trapping" of lipoproteins as well as fat accumulation in the vessel wall [31]. Furthermore, macrophages adherence elevated in during endothelial dysfunction, after they migrate into the intima lining. At this stage, macrophages are known as'foam cells'and become laden with lipids [32].

Whenever, in the LDL molecule, chemical modification occurs, it isknown as oxidation. The oxidation takes place since the chemical reaction occurs due to reactive oxygen species and pro-oxidants, which are produced by macrophages, smooth muscle cells or endothelial cells [23]. Moreover, chronic hyperglycemia also involved in atherosclerotic process sinceglycation of LDL molecule eventually convert LDL into pro- inflammatory molecule. Therefore, this also explains the notationthat diabetes mellitus act as a vital threat of atherosclerosis [31,32].

Endothelial dysfunction

Endothelial dysfunction occurs due to various stimuli including chemical irritants and physical stress, a crucial event in atherogenesis [16]. Activation of endothelial cells is also correlated with different diseasessuch as heart failure, hypertension, diabetes, hypercholesterolemia as well ascigarette smoking.

The disruption ofathero-protective endothelial layer has been reported to be impaired by certain factors. One major factor involved is disturbed blood flow, between bifurcations and arterial branch points.The bifurcation areas including common carotid and left coronary arteries act as major sites for plaque proliferation [33].

Leucocytes activation

Leukocytes activation to the intimal lining is important step in atherogenesis, and it depends on two main factors including expression of leukocyte adhesion molecules (LAM) on the endothelium and chemo attractant signals leading to diapedesis [18]. Both factors not only recruit

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monocytes to the atherosclerotic injury, but also accumulate within plaques during various stages of atherogenesis [34].

Furthermore, the modified form of LDL also acts on endothelial and SMC to produce proinflammatory cytokines. Moreover, these cytokines has been reported to induce LAM as well as chemo attractant cytokine expression. Thereby, modified LDL promote leukocyte recruitment and atherogenesis directly or indirectly [35,36].

Formation of foam cells

Form cell formation is an important step in the promotion the atherogenesis. Monocytes after entering the intimal layer differentiate into phagocytic macrophages, which after absorbing lipoproteins change into foam cells [27]. These foam cells neither recognize nor phagocytose modified LDL, moreover, due to impaired trafficking of foam cells, LDL are accumulated in the plaque, thereby serve as a source of pro- inflammatory cytokines and encourage the plaque progression [36].

Plaque progression

When smooth muscle cells and endothelial cell lining secrete various cytokines and growth factors including interleukins (mainly IL-1), and TNF alpha, the plaque progresses, therefore, atheroma becomes severe leads to vascular tissue impairment [10, 37] . In this condition, fibrous cap is formed due to migration of smooth muscle cell and synthesis of ECM. T lymphocytes, macrophages and collagen-rich fiber tissues contribute in the formation of fibrous cap. Due to all these components atherosclerosis plaque matures, the channel becomes narrow and, therefore, blood stream reduced in the vessels [38].

Smooth muscle cell migration

When SMC migrate from the media layer to the intima layer of blood vessels, it leads to transition from fatty streak to plaque formation [4]. At this time, secretion of extracellular matrix macromolecules occurs asa result ofpropagation of smooth muscle cells within the intima that leads to adheroma. Furthermore, foam cells, activated platelets as well as mediators of endothelium collectively stimulate inflammatory mediators that involved in the migration as well as accumulationof smooth muscle cells into intima. Foam cells not only release certaingrowth factors (GF), and cytokines (CK),however, they also activate smooth muscle cells and leukocytes

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to induce inflammation during the atherosclerotic process [36]. Foam cells also secrete tissue factor that stimulates coagulation in small ruptures and micro thrombus formation in the lesion. These micro thrombi carry activated platelets that further release additional factors such as heparinases and platelet derived growth factors that are involved in local smooth muscle cell movement and proliferation within intima [39].

Common risk factors of atherosclerosis

Dyslipidemia

Dyslipidemia is a proven risk factor responsible for 49% of mortalities worldwide.Abnormally higher lipids in circulation leads to lipids accumulation in the intimallining, thereby enhancing the process of atherosclerosis. It has been reported that countries consuming high amount of saturated fat as well as cholesterol, have significantly high mortality rates from cardiovascular events when these are compared with those having limited consumption of saturated fat and cholesterol levels. One another study indicated that the personshaving total cholesterol level more than 240 mg/dl, are heavily attributed to the coronary risk [40].

Tobacco smoking

It has been observed that smoking accounts for 35% of the risk of atherosclerosis, which further known to be involved in the risk of myocardial infarction and other coronary atery dysfunction [23]. In Atherosclerosis Risk in Communities Study, conducted for continuous three years, the relationof smoking and atherosclerosis development was observed by measuring thecarotid intima-medial thickness inten thousand patients. In this study, a 50% increase in progression of atherosclerosis was reported when compared with nonsmokers.

Cessation of smoking is one of the best effective preventive measures of coronary heart diseases as well as their complications. Soon after stopping the smoking, many cardiac complications due to tobacco use or smoking decrease in a short time interval, moreover, these continue to diminish when cessation was permanently performed [41].

Hypertension (HT)

As it is well known that cardiovascular disease doubles with increase in blood pressure, therefore, elevated HT is an well accepted risk factor for atherosclerosis, including deaths due to

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coronary heart disease or stroke as well [42]. Furthermore, it has been reported that elevated hemodynamic stress results into injury of vascular endothelium is an important mechanisms that elevate the BPand therefore, contributing to atherosclerosis. This injury to endothelium may elevate the permeability of lipoproteins to the intimal wall as well as enhances the development of foam cells leading to progression of plaque formation. Moreover,hypertension also known to increase the atherosclerotic process due to the involvement of Angiotensin II.Ang II, a vasoconstrictor.However, it also as a pro-inflammatory cytokine involved in atherosclerotic process [29,42].

Diabetes Mellitus

Nearly 80% of diabetic patients experiencethree to five folds more atherosclerosis-related cardiovascular problems, therefore, diabetes mellitus is another risk factor of acute coronary events [43].

Certain biochemical pathways have been found to be involved in the progression of diabetic – induced atherosclerosis such as increased synthesis of advanced glycation end-products (AGEs) and reactive oxygen species overproduction. One of the possible mechanism explaining the role of DM in progression of atheroma is non-enzymatic glycation of LDL. AGEs have been involved in enhanced migration of monocytes in subendocardial areas and by elevating the adhesion molecules expression, convert monocytes into macrophages. Further, when glycated LDL are transformed into oxidized LDL, it converts macrophages to foam cells, therefore contribute to related inflammation in atheroma. Moreover, reactive oxygen species are also known to be involved in this process. High blood sugar and free fatty acid stimulate free radical production in endothelial cells and macrophages, leading to coronary endothelium dysfunctions.[80]. Therefore, if hypertension as well as dyslipidemia is properly managed in diabetic patients, it can significantly decrease the risk of cardiovascular events [44].

Lack of physical activity

Studies conducted by INTERHEART have shown that lack of exercise enhances 20% of the chances of angina or infarction. Recent studiesindicate that even with moderate degree of physical exercises may provide protection against coronary dysfunctions [45]. Any type of physical activity not only decreases lipid levels and blood pressure, however, it elevates HDL

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level, enhances insulin sensitivity as well as NO generation by the endothelium, and therebyreduces weight to some extent [40,45].

Overweight or obesity

Owerweight is condsideredone important risk factor for coronary artery disease. Obesity contribute to several other risk factors for atherosclerotic process including hypertension, decreased HDL level, insulin resistance, and hyperlipidemia. Weight loss is an important non-pharmacological treatment to prevent several obesity-related risk factors of atherosclerosis those have just been mentioned [46].

Alcohol consumption

Alcohol if consumed moderately,only 2- 3drinks per day, can produce beneficial effects with regards to coronary heart disease. However, it is harmful when consumed excessively or chronically and may leads to various complications like as liver damage, cardiac failure or neurological complications [87]. Furthermore, binge drinking, also known as irregular heavy drinking has been observed to be associated with increased coronary heart risks.

Family history

A positive family history of atherosclerosis is present in the majority of cases of premature-onset coronary heart diseases.Genetic abnormalities (e.g. familial) are another risk factor. Familial hypercholesterolemia is a condition in which LDL receptors become deficient that cannot properly discard LDL from the circulation [47].

Psychosocial factors

Psychosocial factors have a direct contribution to the early progression of atherosclerosis as itdirectly impairs vessel intima and indirectly exacerbate other complications such as smoking, dyslipidemia and hypertension. In some epidemiologic studies a direct link has been reportedbetween psycho-social factors (such as depressive illness and dispossession) and death due to heart related disorders [91].

Estrogen Status

Risk of cardiovascular diseases is different between men and women throughout life. At young age, malesare prone to 4-5 fold more risk than women, but, this difference does not work at the

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moment of menopause as estrogen secretion reduced to large extent.Estrogen is known to have antioxidant and antithrombotic properties, therefore, improves endothelium-dependent vasodilatation. During premenopause, estrogen contributes to high HDL levels and reduces LDL levels in circulation [49].

Biomarkers

Premature atherosclerosis leads to development of cardiovascular diseases, therefore, identification of associated biomarkers is of great importance. Numerous blood-based biomarkers can serve to recognize patients associated with sub- clinical atherosclerosisincluding homocysteine,lipoprotein A and C- reactive proteins [50].

Homocysteine

A significant positive link between the total serum levels of homocysteine and the prevalence of cardiovascular diseases has been shown in various studies [50,51].Homocysteinecan promotesatherosclerosis by several mechanisms, most important being endothelial dysfunction due to oxidative damage results in disruption of elastic lamina, and intimal thickening due to VSMC proliferation. Moreover, homocysteine also reported to induce mRNA and protein expression of C- reactive proteins in SMC of vessels both in vivo and in vitro [51].

Lipoprotein A

Lipoprotein A is another unbiased threat factor for coronary artery disease. Lipoproteins are complex substancehaving central core comprising cholesterol esters and triglycerides suurounded by free cholesterol, phospholipids and apolipoproteins. The cholesterol content of the lipoproteins has been reported to promote cholesterol deposition in the intimal layer as well as at aortic valve leaflets, results not only into symptomatic atherosclerosis but also in myocardial infarction, angina and ischemic stroke [50]. Furthermore, lipoprotein-A bind to macrophages leading to foam cell production which results in atherosclerotic plaques [36].

Inflammation markers such as C - reactive protein (C-RP)

Several markers of inflammation are reproduced by hepatocytes including CRP, fibrinogen and beta amyloid-A [52]. C-reactive proteins are acute phase proteins with important prognostic value for cardiovascular events including atherosclerosis. During various studies it has been found thatbasal C-RP levels were many folds higher in patients with myocardial infarctionwhen

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compared with controls. C-PR is known to induces the inflammatory condition of atherosclerosis by directing monocytes and lymphocytes to endothelium due to which release ofIL-6 and expression of adhesion molecule increased [50,52].

Conclusion

Atherosclerosis is a disease characterized by formation of fatty streaks, further progresses to atherosclerotic plaques resulting into narrowing and hardening of arteries. Various risk factors and biomarkers of atherosclerosis contribute to its progress and pathogenesis. Several biomarkers, including especially C- reactive protein and homocysteine seem to be promising in the identification of vulnerable atherosclerotic process.However, better understanding of the underlying pathogenesis, risk factors and biomarker indicators will be paramount for the development of treatment strategies targeting atherosclerosis thereby aiming to reduce morbidity and mortality in persons with atherosclerosis.

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