The Role of Inflammation in Atherosclerosis

Boamponsem[1,2], A.G, Boamponsem[3*], L.K

[1]*Department of Biotechnology, School of Biological Sciences, The University of Hull, HU6 7RX. UK*
[2]*Department of Biotechnology, University for Development Studies, Ghana*
[3]*Department of Laboratory Technology, School of Physical Sciences, University of Cape Coast, Ghana*
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ABSTRACT

Atherosclerosis has gained a lot of attention in cholesterol and heart related diseases and is of major concern in cardiovascular health. Most of the research previously conducted on atherosclerosis traced its root cause to high blood cholesterol levels. Emerging studies have drawn attention to immune response and inflammation as very important factors that augment the entire process of atherosclerosis. Research conducted over the years has thrown more light on inflammatory responses in atherosclerosis giving compelling evidences to suggest that inflammation is the key contributor to atherogenesis. Atherosclerotic lesions show similar features of inflammation as those found in typical inflammatory and auto immune disease such as rheumatoid arthritis. Experimental data and results from clinical trials have identified various risk factors including hypercholesterimia, obesity and infection together with biomarkers of inflammation such as C-reactive protein and Interleukin-18 to be associated with atherosclerosis. Most therapies for atherosclerosis produce anti-inflammatory effects. The most knowledge we have on atherosclerosis, the easier it would be to prevent or cure it entirely. This article reviews evidences that lend credence to the proposition that atherosclerosis is an inflammatory disease.

Keywords*: atherosclerosis, artery, hypercholesterimia, obesity, inflammatory response, C-reactive protein, cardiovascular disease.*
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Abbreviations

SMCs: smooth muscle cells, NO: nitrogen oxide, ET-1: endothelin-1, VCAM-1: vascular cell adhesion molecule-1, ICAM–1: intercellular adhesion molecule-1, MCP-1: monocyte chemoattractant protein-1, IFN-γ: γ-interferon, TNF-β: tumour necrosis factor β, MCSF: macrophage-colony stimulating factor, ROS: reactive oxygen species, PDGF: platelet derived growth factor, NFκB: nuclear factor kappaB TF: tissue factor, MMP: matrix metalloproteinases, IL-1: interleukin-1, AII: antiotensin II, Lp(a): lipoprotein (a) , AGE: advanced glycosylation end product, HDL: high density lipoprotein, LDL: low density lipoprotein, oxLDL: oxidized LDL, VLDL: very low density lipoprotein, CRP: c-reactive protein, eNOS: endothelial nitrogen oxide synthase, PAR: protease activated receptor, IL-18: Interleukin-18, LOX-1: lectin-like oxidized low-density lipoprotein receptor-1, Lp-PLA2: lipoprotein-associated phospholipase, HMGCoA: 3-hydroxy-3-methyl-glutaryl-CoA, HMGR: 3-hydroxy-3-methyl-glutaryl-CoA reductase.

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INTRODUCTION

It is predicted that in the next 15 years, cardiovascular diseases arising from atherosclerosis will be the major cause of death globally [1]; prevalence is high in most developed countries and some developing nations [1] and [2]. Cardiovascular disease contributes to 38% of the deaths in North America and is the primary cause of death in European men below the age of 65 while for the women, it falls into second category [1]. Atherosclerosis is the most significant underlying causes of heart failures, coronary artery disease, strokes and infarction (resulting from ischaemia of heart, brain or extremities) [3] and [1].

Atherosclerosis is derived from the Greek words 'athero' meaning paste and 'sclerosis' which means hardening. It can be described as an arterial disease characterized by the formation of atheromatous plaques (composed of cholesterol and macrophages) and the narrowing of the artery (stenosis). Atherosclerosis develops mainly in elastic and muscular arteries that are medium or large in size [4] and [1]. Inflammation is a biological process that occurs in response to stimulus arising from substances (pathogens, damaged cells, toxins, irritants) that pose threats to the survival of cells and the organism as a whole. It involves the immune system (which produces white blood cells to destroy the harmful stimulus) and the vascular system (aids in leukocyte transport into cells). Atherosclerosis develops due factors including failure of the immune system to counteract or destroy modified LDL, free radicals, infectious and or other harmful agents detected by the system as foreign or related diseased conditions [4-9]. The problem emanates from the inability of leukocytes (monocytes and T lymphocytes) to destroy or remove these foreign molecules resulting in the trigger of further immune response which causes the artery to become inflamed [7], [4], [8], [9] and [6]. Inflamed cells produce free radicals, which participate in cell degradation. Atherosclerotic lesions can remain asymptomatic for years and either disappears with time or progress into disease stages where clinical manifestations such as unstable angina pectoris and myocardial infarction can be observed [1] and [3]. Atherosclerosis is a chronic disease since it progresses over years and is cumulative.

In this review, we seek to fully elucidate the role and significance of inflammation in atherosclerosis by examining the structure and function of the artery, mechanisms of atherogeneis and its progression, risk factors, the biomarkers associated with atherosclerosis as well as the treatments available. The therapeutic interventions made by drug discovery and nutrition experts aimed at limiting atherosclerosis or attenuating its sequelae would also be discussed.

2.0 The Artery

Morphological studies of the artery have shown that it is composed of an outer layer (adventia), a tunica media (multiple layers of smooth muscle cells) and an interior (tunica intima) lined with endothelium. When a balance exists between the concentrations of nitrogen oxide (NO: a vasodilator) and endothelin-1, ET-1 (a vasoconstrictor) in the arteries, the endothelium is shielded from injury, inflammation and thrombosis [5]. Also, leukocytes are unable to bind endothelium, smooth muscle cells (SMCs) do not proliferate and platelet aggregation is minimized [5]. However, when risk factors of atherosclerosis set in, the protection conferred on the endothelial cells by such balance is removed since nitrogen oxide production and activity is inhibited.

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3.0 Stages / Disease Progression of Atherosclerosis

3.1 Initiation
The regulatory mechanisms of low density lipoprotein (LDL) receptors function in such a way that the expression of these receptors is halted when the cell has taken up enough cholesterol for its metabolic needs. This is not the situation observed in excessive lipid collection: lipoprotein particles can build up in the intima of arteries as a result of increase in fat diet (cholesterol and saturated fat) in the blood, faulty LDL-receptor control mechanism or genetic defects in LDL-receptor (which causes familial hypercholesterolemia) as described by [6] and [7]. The LDL assembles on the proteoglycan of the endothelium and bind together to form aggregates [8] and [9]. Once attached to the proteoglycan, lipoprotein become highly susceptible to oxidation and other chemical modifications; a very important feature of the pathogenesis of early atherosclerosis [8]. Oxidative stress brought about by NADH/NADPH oxidases of vascular cells, lipooxygenases of infiltrating leukocytes (monocytes and T-lymphocytes) or the myeloperoxidase enzyme can set in at this stage [8]. Oxidized LDL (oxLDL) increases leukocyte adhesiveness and permeability to the endothelium which induces procoagulant instead of anticoagulant properties [4] and [10].
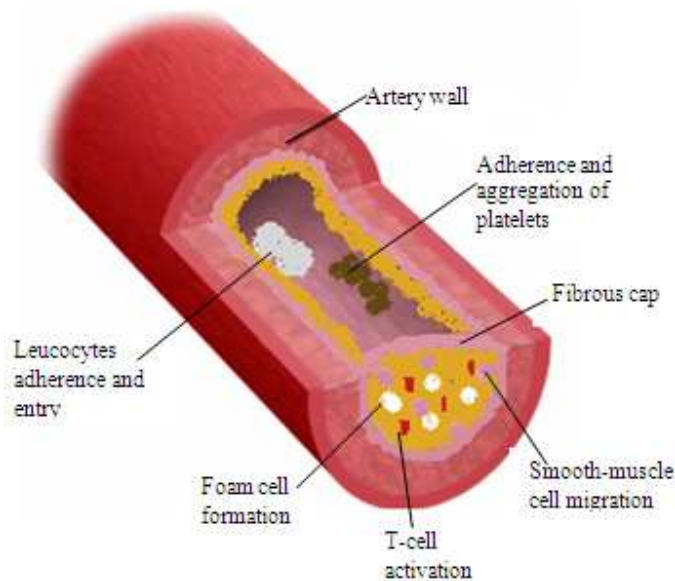

Fig. 1. Leukocyte adhesion and platelet aggregation in the endothelium of the artery together with T-cell activation

The endothelium is induced to express leukocyte adhesion molecules (vascular cell adhesion molecule-1(VCAM-1), intercellular adhesion molecule-1 (ICAM–1) and P-selectins in the development of atherosclerotic lesions [11], [8] and [12]. Signals produced by chemoattractants when monocytes adhere to endothelium (fig.1) allow monocytes to migrate into the arterial wall; monocyte chemoattractant protein-1 (MCP-1) is synthesized by endothelial and SMCs [8], [4] and [11]. VCAM-1 expression rises as atheroma starts to form (fig. 2); this occurrence was observed to be interrupted in genetically modified mice with defective VCAM-1 expression [9]. Experiments conducted using rabbit and mice indicated that VCAM-1 concentration in the endothelium increased prior to leukocyte recruitment [13] and [11]. Subsequent research using MCP-1 mutant mice detected a delay and attenuation in the formation of atheroma when such

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mice were exposed to hyperlipidimic conditions [8].

Dendritic cells, T-cells and mast cells are taken up into the endothelium to assist formation of atherosclerotic plaques; T cells can enter the intima of endothelium by binding to VCAM-1 [11] and [5]. T-cells respond to inflammatory signals by orchestrating the production of γ-interferon (IFN-γ) and the lymphotoxin, tumour necrosis factor β (TNF-β) [11]. These stimulate macrophages, vascular endothelium and SMCs to perpetuate the inflammatory response [11] and [4].
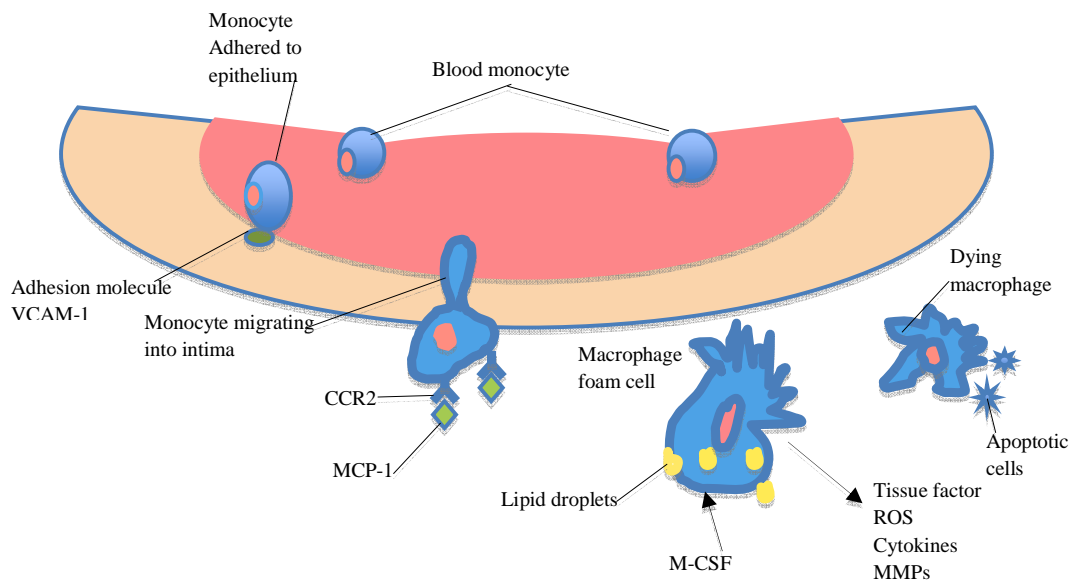

Fig. 2: Attachment of monocytes to VCAM-1 and infiltration of monocytes into sub-endothelial layer of the artery.

3.2 Formation of Foam cells / Fatty Streak

When monocytes are sequestered into the intima, they 'mob up' the modified LDLs to form lipid-laden macrophages (fig.1), a process mediated by macrophage-colony stimulating factor (MCSF) which enables the conversion of monocytes into macrophages [11] and [14]. MCSF facilitates the expression of the scavenger receptor-A family which bind modified LDL to form foam cells by internalizing modified LDL [11] and [8]. MCSF provide a rich source of inflammatory activators such as cytokines (IFN-γ, lymphotoxin, TNF-α), chemokines, eicosanoids and platelet activating factor. Such a phagocytic environment becomes prone to the generation of reactive oxygen species (ROS) like superoxide anion [11] and [8]. When the production of ROS exceeds the host's antioxidant capacity, oxidative stress sets leading to the damage of molecules or cells of the artery [15], [11] and [8]. Continuous inflammation leads to macrophage and lymphocyte activation which results in release of hydrolytic enzymes, cytokines, chemokines and growth factors that cause more damage [4], [9], [11], [10] and [5]. A variety of molecules (oxLDL, bacterial toxins, and remnants from apoptosis) are absorbed into macrophages through scavenger and toll-like receptors. Work done by Bjorkbacka et al. [16] using knockout mice (with deleted apo-E and toll-like receptors) revealed that atherosclerotic lesions did not develop in these mice. They reported that toll-like receptors generated signals that activated macrophages.

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3.3 Atheromatous Plaque
As atherosclerosis persists, a complex lesion is formed from the fatty streak with continuous migration and proliferation of SMC [5], [6] and [8]. When this occurs, an intermediate lesion is formed followed by the thickening and subsequent dilation of arterial wall [4]. Extracellular matrix also accumulates and its dissolution leads to positive remodelling or compensatory enlargement to accommodate arterial growth. Calcification can also occur to further harden the plaque [7]. With time, the activated leukocytes in concert with the arterial cells produce fibrogenic mediators and growth factors that enhance SMC division and subsequent formation of a dense extracellular matrix, a fibrous cap [9]. Platelet derived growth factor (PDGF) secreted by activated macrophages is involved in the high rate of migration and proliferation of SMCs (from the tunica media into the intima) and is over expressed in human atherosclerosis; SMC death is mediated by T-cell, an occurrence which complicates the atherosclerosis plaque [9].

3.4 Thinning and Rapture of Fibrous Cap
At advanced stages of atherosclerosis, activated macrophages decrease the stability of the fibrous cap by producing proteolytic enzymes that breakdown the collagen constituent of the cap (fig. 2). Inflammatory response is perpetuated by CD40/CD40L interaction with activated T-cells and macrophages, an activity that yields tissue factor (TF), matrix metalloproteinases (MMP) and proinflammatory cytokines [11], [5] and [17]. MMP is a protease that cleaves gelatins and type IV collagen component of basement membranes. In the presence of oxLDl, ROS, TFN-α and IL-1 (interleukin-1) within the endothelium, MMP is released from foam cells and SMCs; its proteolytic activity makes atherosclerotic plaques weak and less stable [18]. According to Szmitko et al. [5] and [17], cytokines (TNF-α, IL-Iβ), oxLDL and CD40L are involved in making the fibrous cap thin by enabling over expression of MMP. High expressions of MMP, activated T-cells and TF lead to weakening of the atherosclerotic plaques and to the formation of thrombus respectively [8].

As the fibrous cap grows weaker, it becomes highly susceptible to hemodynamic stresses. Such stress results in disruption of the atherosclerotic plaque which can trigger thrombosis and possibly lead to acute myocardial infarction [5] and [9]. Prothrombotic stimulus is generated when plaques rapture and their contents leak out; lipid spillage causes more inflammation. Dendritic cells in atherosclerotic lesion present antigens to T-cells: modified lipoproteins, heat shock proteins, beta-2-glycoprotein and infectious agents can serve as antigens. Thrombin formation is accelerated as tissue factor, von Willebrand factor and subendothelial collagen (substances whose expression is mediated by IL-1, TNF- α, and CD40L) come into contact with components of blood [5]. As a result, platelets are activated and clump together to form aggregates. More platelets are released and a cycle that amplifies inflammation as well as the disease progression of atherosclerosis is created.

4.0 Triggers and Risk Factors of Atherosclerosis
A number of factors that contribute to the pathogenesis of atherosclerosis have been identified. These factors appear to be closely knitted with inflammatory response or to accentuate it.

4.1 Hypercholesterimia
A high level of LDL cholesterol in the blood is the principal cause of injury to the artery and vascular SMCs [6], [4], [19] and [20]. Defects in the genes that code for LDL-receptors (familial

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hypercholesterolemia), abnormalities in the regulatory mechanisms of LDL-receptors and fatty diet can result in hypercholesterimia [6], [7] and [20] which can eventually lead to atherosclerosis (fig.3).
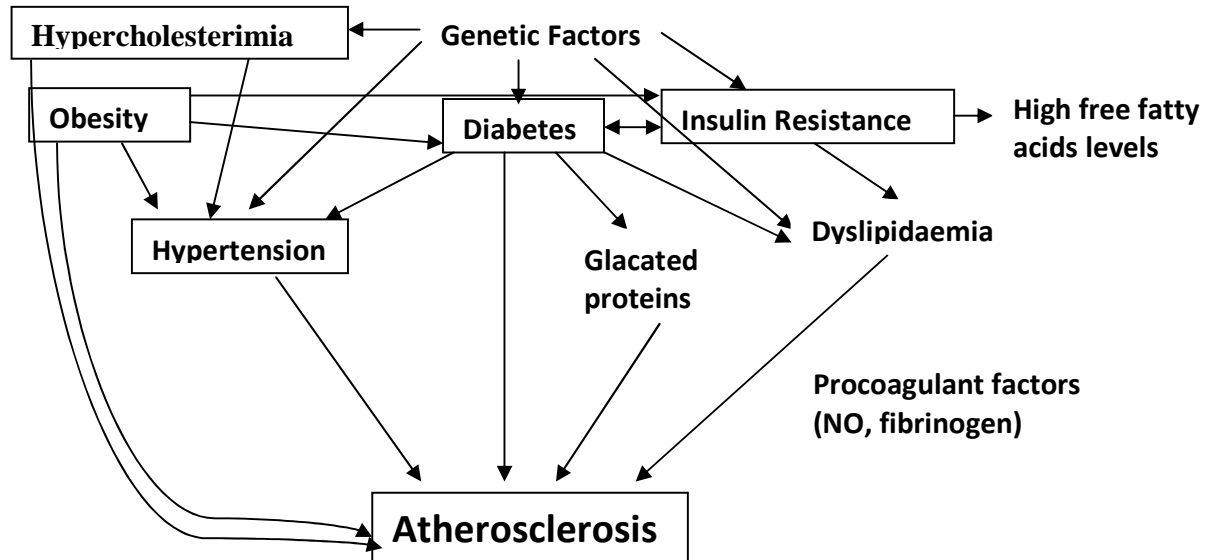

Fig. 3. Pathways and interactions of risk factors of atherosclerosis

Hypercholesterimia appear to activate the inflammatory response by causing expression of mononuclear leukocyte recruiting mechanisms [12] and 21. The gene for VCAM-1 is regulated partly by transcriptional factors influenced by oxidative stress [12]. Mediators of inflammation (TNF-α, IL-1 and MCSF) accelerate binding of LDL to endothelium and SMC by increasing the expression of genes that encode LDL receptors [6] and [7]. With high levels of LDL in vascular endothelium, leukocytes starts to 'cling' to the endothelium and cause further accumulation of lipids which result in foam cells formation [7] and [21]. Further research established that oxLDL has variable biological consequences on the vessel wall: inhibition of endothelial cell vasodilator function, [22] stimulation of cytokine production, [23] and [24] and stimulation of growth factor production.

High density lipoprotein cholesterol (HDL) or "good" cholesterol inhibits oxidative modification of LDL and blocks the proinflammatory effects of oxLDL [14]. HDL provides protection against atherosclerosis by promoting the activity of antioxidant enzymes like platelet activation factor, acetyl hydrolase and paraoxonase [11] and [14]. Studies in transgenic mice show that the key protein of HDL, apolipoprotein A-I, may hinder the oxidation of LDL [25].

Lipoprotein (a), [Lp(a)] resembles LDL but possesses a unique glycoprotein apolipoprotein a (apo a) group and exists in different isoforms with kringle domains that are similar to those found in plasminogen [26] and [27]. An elevated level of Lp (a) is a risk factor for atherosclerosis and coronary heart disease because it promotes inflammation [26-28]. Its activity appears to be facilitated by increased levels of homocysteine, LDL [28] and in diabetics [19]. Apo (a) acts as a ligand that binds specifically to β2-integrin Mac-1; this enhances the recruitment of adhesion molecules and their migration into the endothelium [28]. The authors indicated that through such interaction with Mac-1, Lp(a) induce the nuclear factor kappaB,

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NFκB, (a transcription factor that controls proinflammatory genes) activation resulting in the synthesis of tissue factor (which is prothrombotic) as well as other proinflammatory molecules [27]. Lp (a) inhibits fibrin formation by preventing TGF-β activation [27] and [26]. The physiological role of TGF-β is to restrain inflammatory responses and hinder the migration and proliferation of SMC. Studies involving apo (a) transgenic mice show that apo (a) decreases the amount of plasmin and TGF-β in the aortic wall [27].

4.2 Haemodynamics
Sites of the artery highly susceptible and vulnerable to atherogenesis are the branches, curvatures and bifurcations (areas of hemodynamic strain) where blood flow can be disturbed due to upsurge in turbulence and lowered shear stress [4] and [1]. Haemodynamic strain coupled with lipid accumulation provides a favourable environment for the initiation of atherosclerosis. Low shear stress coupled with increased oscillatory shear stress result in expression of adhesion molecules [1]. At these sites, production of the leukocyte adhesion molecule, ICAM-1, can be stimulated and anti-inflammatory function of nitrogen oxide inhibited [11]. Due to these, SMC synthesis is induced and evokes an inflammatory response.

Sections of the artery that experience laminar flow are less susceptible to atherogenesis; genes that contain shear-stress response elements are present in such regions and have atheroprotective properties since they express enzymes that inhibit VCAM-1 expression [11]. Superoxide dismutase synthesized in areas of laminar flow, catalyzes the breakdown of superoxide anion, a reactive oxygen species, to relieve endothelial cells of oxidative stress [29]. Nitrogen oxide synthase is also a product of these genes; it prevents expression of VCAM-1 through the nuclear factor kappaB (NFκB) pathway [30].

4.3 Hypertension
Angiotensin II (AII) is considered as a powerful vasoconstrictor and plays a role in atherosclerosis by enhancing growth of SMCs [31]. AII speeds up inflammation by facilitating smooth muscle lipooxygenase activity, an activity that yields oxLDL [4]. Free radicals (superoxide anion and hydroxy radicals) generated in the plasma due to hypertensive reactions decrease nitrogen oxide synthesis and increase leukocyte adhesion [32]. AII produced during hypertension can orchestrate inflammation of the endothelial intima causing the endothelium and SMC of the artery to produce superoxide anion [9]. AII and VCAM-1 also promotes expression of cytokines (IL-6) and MCP-1 which serve as activators of inflammation. Hypertension in animal models is associated with leukocyte adhesion, macrophage accumulation, smooth muscle cell migration and proliferation, and intimal thickening [33-35].

4.4 Diabetes
Lipoproteins can undergo glycation in conditions of chronic hyperglycaemia; the modified lipids form advanced glycosylation end product (AGE) which can be recognized by AGE receptors present on macrophages 9] and [15]. Oxidative stress in diabetics is due to the formation of ROS which promotes inflammation [9]. Glycated lipoproteins support the action of proinflammatory cytokines in the arterial endothelium [9]. Insulin resistance in patients with type 2 diabetes leads to hypertriglyceridaemia and dyslipidaemia (fig. 3), conditions that are characterized by low HDL levels with high VLDL (very low density lipoprotein) and LDL levels [19]. In such patients, NO activity is impaired which implies that endothelium function is hindered. Colwell,

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[19] noted that glyco-oxidation, production of free radicals, and reduced antioxidant defence systems are common in diabetics. These enhance lipoprotein oxidation and promote atherosclerosis.

4.5 Obesity

When visceral fat is high, more free fatty acids are generated and this leads to elevated levels of VLDL that can decrease HDL by the action of cholesteryl ester transfer protein which converts HDL into VLDL [9]; high levels of VLDL can instigate atherosclerosis. TNF-α and IL-6 synthesis by adipose tissue participate in inflammation response [9] and [36]. Adiponeotin, leptin and resistin are cytokines produced from adipose tissue which can influence inflammation [1]. These inflammatory processes and high levels of VLDL can bring about atherosclerosis (fig. 3).

4. 6 Smoking

Nicotine and carbon monoxide contents of cigarette have damaging effects on arteries by causing them to lose their compliance and to set up a stage for plaque development. Cigarette smoking results in high levels of circulating non esterified fatty acids which can be injurious to the cell by eliciting inflammatory response [7]. The free radicals generated from smoking results in oxidative stress and increases oxidation of LDL which trigger the recruitment of monocytes and T cells; these lead to formation of macrophages and other processes that promote atherosclerosis [7]. The authors explained that the toxins in tobacco smoke lower a person's HDL while raising levels of LDL cholesterol or "bad" cholesterol.

4.7 Homocysteine

Homocysteine has prothrombotic properties; it inhibits nitrogen oxide activity, it is lethal to the endothelium and increases collagen synthesis [4] and [34]. Severe atherosclerosis was observed in patients with defects in one or both of the enzymes (cystathionine beta-synthase, methylenetetra- hydrofolate) necessary for homocystein metabolism ; most of these patiens had myocardial infarction by the age of 20 [37] .

4.8 Infection

Some Infections (chronic types) that occur outside the vascular system (e.g. gingivitis, prostatitis, bronchitis) and intracellulr infections usually augment the synthesis of cytokines that activate inflammation; these cytokines increase the rate of development of atherosclerotic lesion [9]. Following herpesvirus, cytomegalovirus or *Chlamydia pneumoniae* infection, compliment activation and inflammation can be observed in atherosclerotic plaques [38]. A couple of atherosclerotic plaques isolated from humans were discovered to be infected with *Chlamydia pneumoniae*. The microorganisms synthesize lipopolysaccharides (toxin) and heat shock proteins that incite the endothelium and SMCs to releasse proinflammatory mediators and to facilitate the influx of leukocytes [9] and [36].The authors explained that results obtained from using antibodies raised against *Chlamydia pneumoniae* to predict and or prevent vascular risk have not been conclusive.

5.0 Systemic Indicators of inflammation – Biomarkers

Biomarkers are molecules that serve as indicators of a biological state (e.g. biologic and pathogenic processes) in living systems. Most of the biomarkers associated with atherosclerosis are indicators of inflammatory response.

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5.1 C-Reactive Protein (CRP)

There has been growing evidence to suggest that CRP, an acute phase protein, is a very important biomarker of inflammation. CRPs are vital in predicting atherosclerosis and as such serve as valuable tools in the diagnosis and prognosis of atherosclerosis [38] and [39]. CRP synthesis is induced in the liver by IL-6 and plays a major role in innate immune defences [38] and [36]. To determine whether CRP is indeed present in atherosclerotic plaque, [38], studied the expression levels of CRP and determined that CRP mRNA levels of plaque tissues were 10.2 fold higher than that of normal artery. It was also discovered that there was an up regulation of CRP and complement proteins levels in plaque tissues [38]; CRP promotes complement activation in order to stage an inflammatory response [36].The researchers detected strong signals for CRP mRNA in macrophages and cells. These findings support the hypothesis that CRP may play a direct role in promoting the inflammatory component of atherosclerosis and present a potential target for the treatment of atherosclerosis. CRP prevents nitrogen oxide release into the endothelium by down regulating endothelial nitrogen oxide synthase (eNOS) expression [38] and [40]. Subsequently, CRP enhances the release of endothelin (ET-1), adhesion molecules (VCAM-1, ICAM), chemoattractants (MCP-1), migration of SMCs as well as facilitate LDL uptake by macrophage [38] and [41]. Endothelium responds to CRP by intensifying the release of NFkB which initiates the release of cytokines and mediates cell apoptosis [38] and [5]. According to research by [3], CRP incites processes like angiogenesis inhibition and cell death while it increases ET-1 levels; these disrupt proper functioning of the endothelium.

5.2 Protease Activated Receptor (PAR)

High rates of PAR (G-protein coupled receptor) expression is induced by IL-6 secretion in atherosclerotic lesions and areas of vascular tissue injury [36] and [17]. Of the four types of PAR (PAR-1, -2, -3, -4), it is proposed that PAR-1 activation in the endothelium facilitates the binding of monocytes when NFκB is stimulated - a process that supports ICAM-1 expression [17] and [42]. Likewise, with PAR-3 serving as cofactor, PAR-1 activation promotes leukocyte recruitment in atherosclerosis [17]. PAR-1 and PAR-2 release Weibel Palade bodies which contain p-secretin and von Willebrand factor, molecules that increase the adhesion of leukocytes and platelet to the endothelium [17] and [43]. It has been shown that IL-1 and TNF-α in inflamed cells induce the proinflammatory property of PARs [1]. PAR activity in SMC has been implicated in the translocation of SMCs from media to the intima and collagen synthesis: critical requirements for the formation of fibrous cap [17] and [42]. In vitro experiments using PAR-2 blocking antibody revealed that SMC migration was inhibited [44].

5.3 CD40

CD40 is a protein located on antigen presenting cells and stimulates their activation. CD40 receptor and its ligand, CD40L (on T_H cells), belonging to the TNF family have been detected in atherosclerotic plaques and found to be jointly expressed by activated macrophages, SMCs, vascular endothelial cells and T lymphocytes [45] and [2] . Mice lacking LDL receptors were fed with a high cholesterol diet followed by the introduction of a neutralizing anti-CD40L antibody; the results showed that there was a considerable decrease in the development and progression of atherosclerotic lesions [46]. Such experimental findings lend credence to the claim that the CD40/CD40L is a proinflammatory system; it is linked to atherosclerosis through soluble CD40L (sCD40L) derived from activated platelet [47]. It is reported that in patients with

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moderate hypercholesterolemia and type 1 or 2 diabetes, higher amounts of sCD40L has been identified [48] and [49]. Binding of sCD40L to CD40 on SMC and endothelium initiates a cascade of events that lead to endothelial dysfunction and inflammation. ROS formed due to CD40 and CD40L binding antagonises the activity of NO causing a decline in its synthesis [17]. In response to this, proinflammatory cytokines (IL-6, IL-1), VCAM-1, ICAM and MCP-1 are produced [17] and [2] .
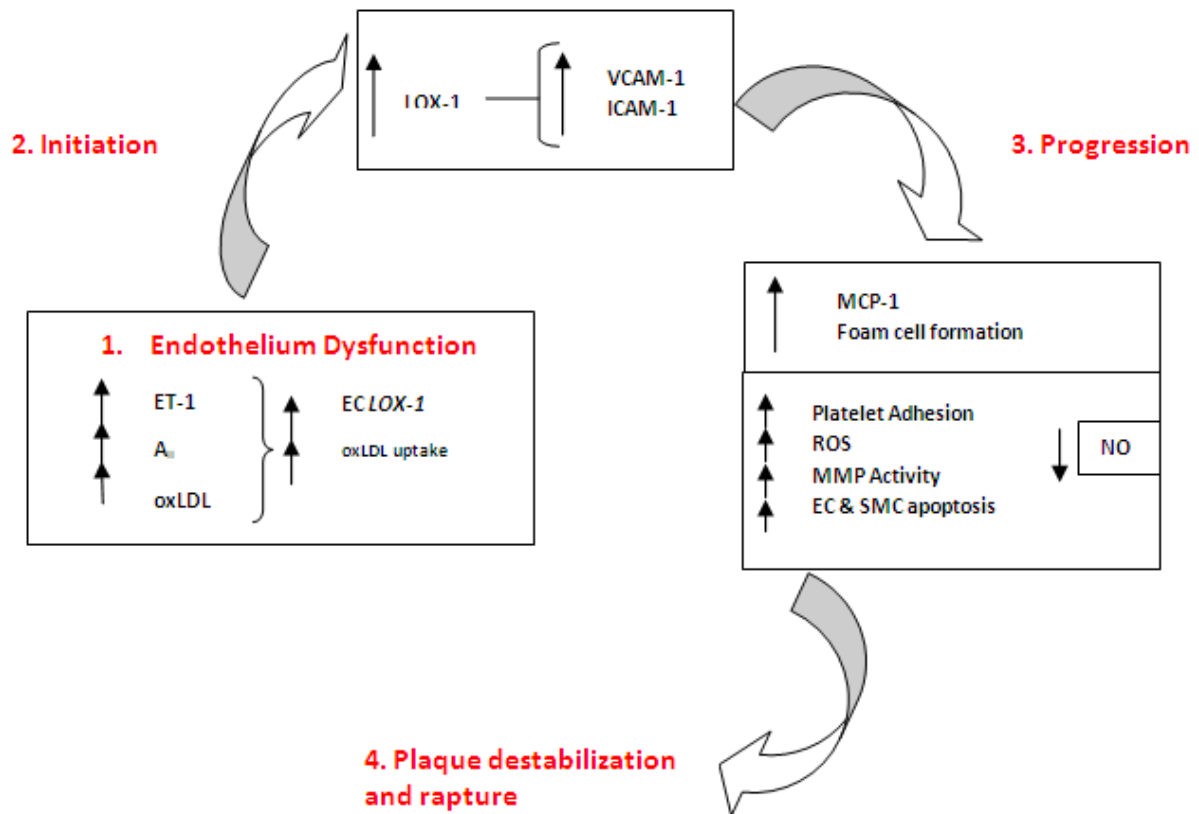

Fig. 4. Flow chart showing mechanism of the various processes and inflammatory responses involved in the generation and maintenance of atherosclerosis with reference to the typical biomarker, LOX-1.

5.4 Interleukin-18
Interleukin-18 (IL-18) is a cytokine that is made by macrophages; IL-18 binds to its receptor expressed on lymphocytes (T-helper (Th) 1), ECs, SMCs, and macrophages [50]. Cytokines (IL-1, TNF-α, and IL-6) prompt IL-18 gene expression in macrophages and leukocyte adhesion is increased as more IL-I8s are synthesized since IL-18 accentuates VCAM-1 and ICAM-1 levels [5]. IL-18 binds to its receptors and primes the production of its activators (IL-1β, TNF-α) to establish a positive feedbback mechanism that perpetuates inflammation and plaque formation. Plaque stability is lowered because IL-18 causes an increase in MMP expression [5]. Blankenberg et al [51], reported that the quantities of IL-18 detected in patients with myocardial infarction or unstable angina were greater than in normal patients. Research done by [52] using apolipoprotein E–deficient mice revealed that when exogenous IL-18 was introduced into such mice (at constant serum cholesterol concentrations), there was an increase in the size of atherosclerotic lesion and the number of lesion-associated T cells.

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5.5 Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)

LOX-1 is expressed in endothelial cells, macrophages and SMCs. LOX-1 recognises and binds specifically to oxLDL [53]. High levels of LOX-1 have been detected in all stages of atherosclerosis; its production is mediated by A_{II} and ET-1 [17]. LOX-1 has been discovered to also bind apoptotic cells, activated platelets, advanced glycation end products, and pathogenic organism [54]. LOX-1 provides a route of entry for oxLDL into endothelium, an action that disrupts normal endothelial function by encouraging monocyte adhesion and infiltration (fig. 4). With regards to studies undertaken by [55] and [17], the oxLDL/LOX-1 complex enhances ROS production, death of SMCs and MMP influence on fibrous cap.

5.6 Lipoprotein-associated phospholipase (Lp-PLA$_2$)

Results from in-situ hybridization and immunohistocompatibility studies indicate that macrophages in rabbit and human atherosclerotic lesions expressed LpPLA$_2$ [56]. There has been some evidence to suggest that LpPLA$_2$ has proinflammatory and proatherogenic functions by generating lysophosphatidylcholine (lysoPC) and non-esterified fatty acid moieties [57]. LysoPC promotes monocyte chemotaxis and increases expression of mononuclear leukocyte adhesion molecules in endothelial cells; LysoPC is suspected to facilitate initiation of atherosclerotic lesion through such activities [17]. The authors suggest that lysoPC binds to peptides and become antigenic and in turn, stimulate T cells.

6.0 Treatment

Since inflammation has been implicated as the central mechanism for the pathogenesis of atherosclerosis, most therapies are designed to produce anti inflammatory effects.

Antioxidants (e.g. vitamins A, C, E) are known to have anti-inflammatory effects on cells. Studies carried out indicate that antioxidants reduce fatty streaks in arteries of animals and improves the resistance of human LDL (in vitro) to oxidation [58] and [59]. Administration of high doses of vitamin E (α-tocopherol) reduces the release of proinflammatory cytokines levels and decreases adhesion of monocytes to endothelium [60]. Vitamin E reduces CRP levels in patients with cardiovascular disease and in those with risk factors for it [58] and [59]. Vitamin E enrichment has been found to hinder LDL oxidation, inhibit platelet adhesion and aggregation, restrain the increase of smooth muscle cells, slow down the expression and function of adhesion molecules, attenuate the production of leukotrienes and increase the release of prostacyclin by means of up-regulating the expression of cytosolic phospholipase A2 and cyclooxygenase [58-61]. Cooperatively, these biological functions of vitamin E could account for its shielding effect against the development of atherosclerosis. An imbalance between oxidative stress and antioxidant status is present in patients with advanced atherosclerosis [61]. Vitamin E supplementation improves this imbalance in plasma but not in plaques [62] and [61] Peluso, [63], proposed that flavonoids act in the artery wall to repress LDL oxidation caused by macrophages and inflammatory responses; intake of flavonoids resulted in a decline in coronary heart diseases. There are six main classes of flavonoids (flavanones, flavones, flavonols, isoflavonoids, anthocyanins, and flavans); flavanones occur mostly in citrus fruits, flavones in herbs, isoflavonoids in legumes, anthocyanins and catechins in fruits and flavonols in all fruits and vegetables. Flavonoids in plants (soybean isoflavones) and in red wine decrease ROS production and maintains or enhances the balance between NOS and ET-1 in the endothelium [63]. By performing this role, flavonoids help to maintain normal vascular cell functions. Anthony et al

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[64] found out that atherosclerosis is lessened in animals fed diets containing soy protein compared with those fed diets with animal protein. Probable mechanisms by which soy isoflavones may avert atherosclerosis include a favourable effect on plasma lipid concentrations, antiproliferative and antimigratory effects on smooth muscle cells, effects on thrombus formation, antioxidant effects and maintenance of normal vascular reactivity [64].

Statin is a drug administered to patients with atherosclerosis. It inhibits cholesterol synthesis by inactivating the rate limiting enzyme, 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR) responsible for the formation of mevalonate from HMGCoA [6]. Cholesterol synthesis is halted because other isoprenoids necessary for the process cannot be formed. Statin has a positive effect on eNOS mRNA expression while it inhibits the production of ET-1; these assist in establishing the balance required for the proper functioning of the endothelium (i.e. less vasoconstriction and more relaxation). The administration of statin to patients with hyperlipidemia resulted in a considerable decrease in CRP concentrations [10]. Reduced NFkB activity was observed in circulating mononuclear cells in the presence of statin, an indication that proinflammatory genes were being suppressed [10].

CONCLUSION

Inflammation participates in all stages of atherosclerosis; all risk factors of atherosclerosis as well as the disease progression have been shown to elicit inflammatory response. Clinical trials, laboratory experiments on animals and tissues in conjunction with population studies have yielded vital clues that lend credence to the claim that atherosclerosis is a chronic inflammatory disease. Atherosclerosis is evidently an inflammatory disease and does not result merely from the build up of lipids: macrophage colony-stimulating factor plays a key role in the regulation of the amounts of macrophages and monocytes and in lesion formation but lipids and other molecules have minimal effect on atherosclerosis development.

Theapeutic measures designed to target the inflammatory mechanisms as well as healthy lifestyles (e.g. good nutrition, exercise) can curb or completely eliminate atherosclerosis. The possibility that members of this class of compounds might also ameliorate hypertensive vascular injury deserves further investigation.

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