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Atherosclerosis: Pathophysiology and Management

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ABSTRACT

Background: Atherothrombotic cardiovascular disease is currently the leading cause of morbidity, mortality and cost burden in the medical community. New studies have found atherosclerosis to be predominantly an inflammatory reaction of vessel wall. **Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through February 2017. The following search terms were used: Atherosclerosis, thrombotic heart diseases, hypertriglyceridemia, dyslipidemia, pathology of atherosclerosis, treatment of atherosclerosis. **Aim:** In this review, we evaluated the pathogenesis, risk factors and management of atherosclerosis.

Conclusion: More studies must be done to offer better management, even though massive success was achieved in the past decades. Also healthy population must be encouraged to avoid risk factors that cause such pathologies.

Keywords: hyper triglyceridemia, dyslipidemia, pathology of atherosclerosis, treatment of atherosclerosis

INTRODUCTION

Atherosclerosis is described as a chronic inflammatory reaction of the wall of vessels in response to dyslipidemia along with endothelial distress including the inflammatory recruitment of leukocytes with the activation of local vascular cells. The chronic inflammation of arterial vascular wall is believed to cause multifocal plaque development.

Most plaques stay asymptomatic in a subclinical state, some become obstructive causing stable angina, but a few become thrombosis-prone which are vulnerable and lead to atherothrombotic events including acute myocardial infarction (AMI), stroke and ischemia of lower limb[1].

Atherothrombotic cardiovascular disease (CVD) is currently the leading cause of death and morbidity not only in rich countries but world-wide and, therefore, has a large economic burden and public health impact.Fortunately, the mortality of atherothrombotic CVD has fallen dramatically in the past several years, causing prolonged survival with chronic disease, which in turn explains the reason why prevalence, burden, and costs of this disease has become high[2].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1987, through February 2017. The following search terms were used: *Atherosclerosis, thrombotic heart diseases, hypertriglyceridemia, dyslipidemia, pathology of atherosclerosis, treatment of atherosclerosis*

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board Imam Abdulrahman Bin Faisal University.

PATHOPHYSIOLOGY

Hypercholesterolemia is noted as one of the chief triggers of atherosclerosis. The rise in plasma cholesterol levels causes changes inpermeability of arterial endothelial cells that allows the migration of lipids, particularly LDL-C particles, inside the arterial wall. Circulating monocytes stick to the endothelial cells that express adhesion

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molecules, for example vascular adhesion molecule-1 (VCAM-1) and selectins, and, subsequently, migrate with the help of diapedesis into the subendothelial space [3]. Once they reach the subendothelial space, the monocytes gain macrophage characteristics and transform into foamy macrophages. LDL particles in the subendothelial space are oxidized and grow into strong chemo-attractants. These processes only heighten the build up of massive intracellular cholesterol facilitated through the expression of scavenger receptors including A, B1, CD36, CD68, for phosphatidylserine, and oxidized LDL by macrophages, which in turn bind the native and modified lipoproteins to anionic phospholipids. The end outcome is a cascade of vascular modifications which comprise formation of a fatty streak, intimal thickening, and eventually fibro-atheroma and plaque buildup. The clinical sequelae of atherosclerosis are vessel narrowing with symptoms such as angina pectoris and acute coronary syndromes as a result of plaque instability[4].

The majority of coronary thrombi are produced by plaque rupture (55–65%), after that by erosions (30–35%), and seldom from calcified nodules (2–7%). Rupture-prone plaques usually contain a soft, large, lipid-rich necrotic core with aninflamed and thin (≤65 μm) fibrous cap. Other shared features consist of expansive remodeling, neovascularization, large plaque size (>30% of plaque area), plaque hemorrhage, inflammationof adventitial, and spots of calcifications. Susceptible plaques contain monocytes,T cells, and macrophages. T-cells encourage the vulnerability of plaques by their effects on macrophages[5].

Macrophages and Atherosclerosis

Macrophages are greatly adaptive cells, which respond to a plenty of environmental signals comprising microbial products as pathogen-associated molecular patterns (PAMPS), cytokines, chemokines, activated or damaged cells, biologically active lipids substances, and modified endogenous biomolecules such as danger-associated molecular patterns (DAMPs) by obtaining distinct functional phenotypes and regulating their metabolism to tolerate their specific bioenergetic request. While Th1 cytokines like IFNγ and IL-1β, or bacterial products such as lipopolysaccharide (LPS) prompt a 'classical' proinflammatory M1 phenotype, the Th2 cytokines, including IL-4 and IL-13, trigger an 'alternative' anti-inflammatory response and reparatory M2 phenotype[6].

Chronic inflammation is the primary hallmark of atherosclerosis. Macrophages, apparently of the M1 phenotype, are significant sources of proinflammatory mediators that provoke the recruitment and the activation of supplementary macrophages along with other immune cells thus constantly promoting inflammation and progression of plague. In contrast, M2 macrophages are the sources of anti-inflammatory mediators and may inhibit inflammation as well as atherosclerosis development[5].

Inflammation and Atherosclerosis

Atherosclerosis was once believed to be a cholesterol deposition disease, but newer evidence show that involvement of the immune system and chronic inflammation essentially contributes to atherosclerotic lesion progress[7]. A vital step in atherosclerosis beginning and development is the recruitment of monocytes into the artery wall. There the monocytes differentiate into macrophages, ingest the lipoproteins, remove dead cells and debris, and ultimately turn into foam cells. Not much is known about the metabolic variations of macrophages to the constantly changing microenvironment during the period of atherosclerosis initiation and plaque development[7].

In examining the microenvironment in an atherosclerotic plaque, it contains pro-inflammatory cytokines,cholesterol crystals, high levels of oxidatively modified lipids, and a diversity of DAMPs which was released by dying cells. Such inducers of inflammation possibly also change glucose utilization by macrophages. Furthermore, reactive oxygen species (ROS) are found in great quantity in atherosclerotic plaques, where they have the ability to damage proteins, lipids and DNA, thus affecting cellular metabolic activity. ROS can also encourage mitochondrial damage causing a progressive respiratory chain dysfunction, which in sequence has strong consequences on the energetic profile of macrophages. Additionally, the growth of atherosclerotic plaques is escorted by hypoxia along with activation of HIF-1α. Nevertheless, the association between the inflammatory status and the bioenergetic profile of plaque macrophages and its impact on atherosclerosis progression or regression staysmostly unknown[8].

Platelets and Atherosclerosis

Platelet adhesion occurs under conditions of high shear stress, as in stenotic atherosclerotic arteries. This is essential to the development of arterial thrombosis; hence, particular control of platelet adhesion is required to maintain blood fluidity and to prevent thrombosis or other hemorrhagic complications.Despite their central role in hemostasis and thrombosis, platelets significantly contribute to the initiation, progression and exacerbation of atherosclerotic plaques via their secretory functions.As central modulators of inflammatory and immune responses the part of platelets in coagulation and in plaque stability yet remains to be understood[9].Most remarkably, plaque progression and inflammation is stimulated by deposition along with synergistic functions of platelet chemokines for example, RANTES/CCL5, on the arterial surface activating monocyte arrest and macrophage infiltration. Clinically, increased plasma levels of CCL5 precisely predict refractory symptoms and upcoming events in case of unstable angina pectoris. Therefore, platelets and coagulation seem to have up till now underappreciated effects on plaque stability and following complications. Though, experimental studies intensely support the validity of anti-inflammatory methods to endorse plaque stability[10].

Angiogenesis in Atherosclerotic Plaques

The development of atherosclerotic plaques is linked with the appearance and growth of the vasa vasorum. In humans plaque microvessel content upsurges with plaque advancement and is to be expected stimulated by hypoxia of plaque, hypoxia-inducible factor (HIF) signaling, ROS or other inflammatory signals.The occurrence of plaque hypoxia is principally determined by plaque inflammation due to increasing oxygen demand, while the influence of plaque thickness through reducing oxygen supply seems to be an insignificant factor. Plaque microvessels are immature and delicate and the inaccurate integrity of microvessel endothelium likely causes intra-plaque hemorrhage,thus placing plaques at increased risk for rupture[11].

The histological recognition of intra-plaque hemorrhage is linked with plaque rupture. Nevertheless, it remains to be established, whether the intra-plaque hemorrhage from neo-vessels elicits plaque rupture or vice versa. Nonetheless, adventitial microvessels are obviously related to atherosclerotic disease[10].

Hyperglycemia and Atherosclerosis

When observing into macrophage glycolytic profile in atherosclerosis, the character of glucose availability in the environment could be vital for the growth of atherosclerosis. Remarkably, diabetes intensely predisposes to atherosclerosis. Nevertheless, mechanisms that endorse and hasten atherosclerosis in diabetes are not well understood. Hyperglycemia related with type 1 or type 2 diabetes mellitus is a strong and an independent risk factor for atherosclerosis and subsequent cardiovascular events. Amplified inflammatory activation of macrophages is the hallmark of diabetes. Hyperglycemia and increased glucose obtainability would favor amplified glucose flux and glycolysis in macrophages, causing the macrophage inflammatory activation. Fascinatingly, monocytes or macrophages exposed to increased glucose concentration present an M1 profile[12].Additionally, Glut1 overexpression by growing glycolysis drives a proinflammatory phenotype analogous to M1 macrophages. Moreover, hyperglycemia endorses myelopoiesis and damages the resolution of atherosclerosis, while lowering hyperglycemia has been noted to decrease monocytosis, migration of monocyte into atherosclerotic plaques, and to promote plaque reversion. Increased glucose levels promote leukocyte-endothelial cell migration and interactions which are important for atherosclerosis initiation[13].

Consequently, it has been suggested that glucose control could be an effectual strategy to decline the risk of atherosclerosis in diabetic patients. Nevertheless, even though in type 1 diabetic patients' control of glycemia decreased major cardiovascular events, several studies which were conducted on type 2 diabetic patients presented that glycemic control did not result in a lessening of cardiovascular events. This could be as a result of the fact that type 2 diabetes habitually is concomitant with other cardiovascular risk factors including obesity, hypertension, and dyslipidemia, which could disguise the favorable effects of glucose lowering. These findings suggest that increased glucose obtainability may not be sufficient to drive macrophage-mediated inflammation;nonetheless, elevated glucose may donate to potentiate

inflammation, predominantly in high glucose-demanding cells for instance activated M1 macrophages[12].

Intestinal Microbiome and Atherosclerosis

Recent studies indicated that a significant interaction between nutrition and the intestinal microbiome brings into play further metabolic factors that exacerbate atherosclerosis outside dietary cholesterol. This may help to enlighten the benefits of the Mediterranean diet. It was reported that phosphatidylcholine found in egg yolk and carnitine from animal flesh which is four times higher in red meat compared to fish or chicken are transformed by intestinal bacteria to trimethylamine which is the compound that causes uremic breath to smell fishy[14].Trimethylamine is oxidized in the hepatocytes to trimethylamine N-oxide (TMAO), which leads to atherosclerosis in animal models. In patients who were referred for coronary angiography, high levels of TMAO after a test dose of two hard-boiled eggs significantly increased risk. Patients in the top quartile of TMAO had a 2.5 times increase in the three year risk of stroke,myocardial infarction, or death. Therefore, patients at risk of cardiovascular disease must limit their consumption of meat and egg yolk not merely because of the high cholesterol content but also due to the carnitine in meat (predominantly in red meat) and the phosphatidylcholine found in egg yolk. This is chieflysignificant in patients with renal failure[15].

A significant issue is that vegans who ate L-carnitine did not produce TMAO because they did not have the intestinal bacteria that create TMA from carnitine; this demonstrates that the intestinal microbiome is adjustable. A novel approach to managing atherosclerosis would be the extermination of harmful bacteria with the help of antibiotics and recolonization of the beneficial bacteria by stool transplantation. This is totally analogous to the management ofClostridium difficile infection by repopulation[15].

PREDICTORS AND RISK FACTORS

Risk factors recognized include hypertension, diabetes,smoking, left ventricular hypertrophy, and elevated LDL. LDL-C, TG and HDL-C appeared as powerful independent predictors of atherosclerotic disease following the analysis of the data from the Framingham study[16]. While the influence of other parameters is being examined, TC, LDL-C and HDL-C continue to date the cornerstone in risk approximation for future atherosclerotic events. Low HDL-C has been presented to be a strong independent conjecturer of premature atherosclerosis and is involved in most of the risk estimation scores system. Very high amount of HDL-C, conversely, have dependably not been found to be linked with athero-protection. The mechanism by which HDL-C shields against atherosclerosis is still under discussion and gathering evidence strongly recommends that the proportion of dysfunctional HDL and functional HDL rather than the levels may be of significance[17].

Hypertriglyceridemia (HTG) has been noticed to be another independent risk factor for cardiovascular disease. Furthermore, high TG levels are often concomitant with low HDL-C and high levels of small dense LDL particles. The affliction of HTG is remarkable; with about one-third of adult individuals having TG levels over 1.7 mmol/l (150 mg/dL)[18].

Lp(a) is a specialized form of LDL and contains of an LDL-like particle and the precise apolipoprotein (apo) A. Elevated Lp(a) is an extra independent risk factor while genetic data made it a likely cause in the pathophysiology and development of atherosclerotic vascular disease as well as aortic stenosis[19].

MANAGEMENT

LDL Lowering Therapy

1. HMG-CoA reductase inhibitors (statins)

3-hydroxy-3-methyl–glutaryl-coenzyme A (HMG-CoA) reductase inhibitors commonly named as ‘statins’ prompt an augmented expression of LDL receptors (LDL-R) on the surface of the hepatocytes, which leads to an increase in the uptake of LDL-C from the blood and a reduced plasma concentration of LDL-C along with other apo B-containing lipoproteins, together with TG-rich particles. Statins are often very effective drugs that in an overwhelming quantity of well conducted clinical trials displayed consistent clinical event decreases with a very good safety profile.

On the other hand, side effects of significance may occur making the compound, as in any drug class, sometimes inappropriate for individual patients[18].

2. Cholesterol absorption inhibitors

By decreasing cholesterol absorption, ezetimibe decreases LDL-C. Results support the use of ezetimibe as second-line therapy in connotation with statins when the therapeutic goal is not attained at the maximum tolerated dose of statin, in statin-intolerant patients, or in patients who have contraindication to statins[20].

3. Bile acid sequestrants

At the maximum dose, cholestyramine, colestipol or the newly established colesevelam can produce a decrease in LDL-C by 18–25%. The use of cholestyramine and colestipol is restricted by gastrointestinal adverse effects and some major drug interactions with other habitually prescribed drugs. Colesevelam, however, seems to be better tolerated and to have less interaction with other drugs and so can be taken together with statins. Comparatively little evidence is presented from large clinical trials for this class of drugs[21].

4. Proprotein convertase subtilisin/kexin type-9 inhibitors

Inhibitors of proprotein convertase subtilisin/kexin type-9 (PCSK-9) give the prospect of accomplishing even lower LDL-C levels than statins when combined with ezetimibe. PCSK-9 binds to LDL-R at the hepatocytes and stimulates the absorption and also the degradation of these receptors. Through inhibition of PCSK-9, the degradation of LDL-R is prohibited thereby increasing the absorption by the liver of LDL-C particles, which subsequently leads to lower LDL-C plasma concentrations[22].

TG Lowering Therapy

1. Statins

Statins decrease the plasma concentration of TG-rich particles by inhibiting HMG-CoA reductase.

Even though recent evidence positions HTG as a cardiovascular (CV) risk factor, the advantages of lowering elevated TG levels are still not sufficient.Statins are the first-choice treatment in patients with HTG since they decrease both the CV risk and, in high doses, have a tougher effect on elevated TG levels causing up to 27% reduction[23].

2. Fibrates

Fibrates are peroxisome proliferator-activated receptor-α (PPAR-α) agonist, acting through transcription factors regulating many steps in lipid and lipoprotein metabolism. Fibrates have decent effectiveness in depressing fasting TG as well as post-prandial TGs and TG-rich lipoprotein remnant particles, with decreasing TG levels up to more than 50%[24].

3. n-3 fatty acids

N-3 fatty acids, which include eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA), can decrease TG possibly by interaction with PPARs. Even though the underlying mechanism is not understood well, n-3 fatty acids can decrease TG levels with up to 45%. If TG are not controlled by statins or fibrates n-3 fatty acids may be taken additionally to decrease TG further, as these combinations are generally safe and well tolerated[23].

Anti-platelet Therapy

Anti-platelet therapy might stabilize the vulnerable patient by decreasing the amount of localized thrombus formation as well as decreasing vascular inflammation. Aspirin has been shown to be beneficial for secondary prevention in patients with recognized atherosclerotic vascular disease. Out of the four commonly recommended remedies for secondary prevention (which includes statin, aspirin, angiotensin-converting enzyme inhibitor,β-blocker), the combination of statin with aspirin are linked with the greatest decrease in mortality in a case-control analysis. In addition to aspirin, there is also promising evidence for other anti platelet agents for instance prasugrel, clopidogrel, and ticagrelor[25].

Anti-hypertensive Therapy

B-blockers have been recognized to reduce recurrent AMI, sudden cardiac death and overall mortality in patients with acute myocardial infarction in several clinical trials. They decrease heart rate and blood velocity making the flow less turbulent and also lower wall stress. A recent pooled analysis of four IVUS trials has demonstrated that β-blockers delay the development of atherosclerosis.Angiotensin II is a pro-inflammatory cytokine which supplements the production of ROS. Blocking angiotensin II has therefore reduces signs of inflammation in atherosclerotic animals. Renin-angiotensin system inhibition also recovers endothelial function[26].

CONCLUSION

As we have seen in the review that cardiovascular atherosclerotic disease remains the leading cause

of worldwide morbidity, mortality, and economic burden, more studies must be done to offer better management, even though massive success was achieved in the past decades. Also, the healthy population must be encouraged to avoid risk factors that cause such pathologies.

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