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A REVIEW ON MANAGEMENT OF ATHEROSCLEROSIS

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ABSTRACT

Atherosclerosis is a leading cause more mortality and morbidity in worldwide. The underlying pathogenesis involves an imbalanced lipid metabolism and a maladaptive immune response entailing a chronic inflammation of the arterial wall. New pro and anti-inflammatory pathways linking lipid and inflammation biology have been discovered, and genetic profiling studies have unveiled variations involved in human coronary artery disease. The growing understanding of the inflammatory processes and mediators has uncovered an intriguing diversity of targetable mechanisms that can be exploited to complement lipid-lowering therapies. Here we aim to review the recent developments and clinical strategies for the management of atherosclerosis.

KEYWORDS

Atherosclerosis, Inflammation and Coronary artery disease.

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INTRODUCTION

Atherosclerosis is the major cause of morbidity and mortality in the developing and developed countries[1]. South Asians around the globe have the highest rates of Coronary Artery Disease[2]. According to National Commission on Macroeconomics and Health, a government of India undertaking, there would be around 62 million patients with Coronary Artery Disease by 2015 in India and of these, 23 million would be patients younger than 40 years of age[3].

Atherosclerosis, the underlying cause of a wide spectrum of cardio vascular disease outcomes, involves a complex pathologic process thought to be initiated principally at sites of endothelial

dysfunction, by the retention, accumulation, and oxidative modification of lipoproteins in the arterial wall[4]. This process is enhanced in hyper cholesterolaemic patients as penetration and retention of low density lipoproteins in the arterial intima is increased, thus providing higher levels of substrate available for generation of oxidatively-modified, proinflammatory LDL[5]. The first stage in atherogenesis involves the formation of fatty streak lesions in the arterial intima. Such initial lesions are composed predominantly of cholesterol-rich, monocyte-derived, macrophage foam cells, which typically result from the avoid uptake of modified forms of cholesterol-rich LDL, but may similarly be driven by uptake of native VLDL[6]. These cells exhibit a proinflammatory, prothrombogenic phenotype[7]. The lesion evolves as further inflammatory and immune cells are recruited from the circulation, with concomitant migration of smooth muscle cells from the outer layers of the arterial wall; such cells may equally take up native and/or modified lipoproteins (including VLDL and LDL) with transformation to foam cells. As the lesion progresses, cytotoxic factors such as oxysterols can induce apoptotic, necrotic or autophagic cell death in inflammatory and immune cells, there by stimulating the release of both intracellular content and microvesicles. Consequently, intermediate lesions typically progress towards an advanced plaque comprising a necrotic core of cellular debris together with lipoprotein-derived lipids beneath a fibrous cap. Thin, inflammatory fibrous caps are prone to rupture under mechanical stress; rupture may equally be potentiated by intraplaque haemorrhage. Plaque fissure constitutes a key trigger of thrombosis as plaque contents, and notably monocyte macrophage-derived micro particles containing tissue factors[8], are exposed to circulating procoagulant factors. Consequently, the clinical complications of CVD ensue[9].

It is now recognised that a major factor in driving atherogenesis is an enhanced immuno-inflammatory response in the vascular wall, for which minimally, moderately or extensively oxidised LDL may act as the initial stimulus. Such an inflammatory response, initiates the oxidative stress and perturbation of lipid metabolism[10]. Moreover, the major cardio vascular risk factors, including hypertension, dyslipidaemia, diabetes and smoking, mutually interact at the endothelial surface to exert vasculotoxic effects, which may act synergistically to induce endothelial dysfunction [11, 12]. Importantly, elevated levels of oxidised LDL have been documented in individuals presenting with mild to moderate hypertension[13]. Moreover, hypertensive individuals have been reported to present a proatherogenic, dense LDL phenotype [14, 15]. Consistent with these observations, patients with elevated blood pressure display accelerated atherosclerosis as compared with individuals exhibiting “normal” levels of blood pressure; in addition, antihypertensive agents have been shown to slow plaque progression[16-18].

CAUSES OF ATHEROSCLEROSIS

Atherosclerosis affecting the coronary arteries is due to compromise blood flow leads to chest pain (Angina pectoris), or if the conducting system of the heart is involved, disturbances of the heart’s rhythm occur. A blood clot may form over an atheromatous lesion leading to total occlusion of the artery and hence ischaemia of the heart muscle served by that artery leading to myocardial infarction[19]. In epidemiological studies, three major risk factors for coronary heart disease (atherosclerosis) have been identified: hypertension, cigarette smoking and total plasma cholesterol concentration and minor factors like diabetes mellitus, obesity and stress, physical inactivity, family history and increased triglyceride levels.

ATHEROMA FORMATION

The initial step in atheroma development is infiltration of the arterial wall by lipoprotein particles and their subsequent entrapment in the intima. Entrapment may occur by interaction of the

protein component of LDL with substances such as glycosaminoglycans within the intima, or the lipoprotein may be chemically modified by oxidation or glycation or by the attachment of malondialdehyde. These modified lipoproteins are taken up by macrophages by a receptor dependent mechanism which does not involve the LDL receptor. This 'scavenger receptor' is not down regulated by the presence of excess intracellular cholesterol (unlike the LDL receptor) and therefore continued uptake of modified LDL occurs, giving rise to intracellular cholesterol droplets. The mature atherosclerotic lesion is termed the fibrous plaque; this result from proliferation of smooth muscle cells and their stimulation to produce collagen. Growth factors responsible for smooth muscle cell proliferation are produced by macrophages, endothelial cells and platelets. Whilest the endothelium over the plaque remains intact, circulating platelets do not come in to contact with the subendothelial layer but occasionally the plaque ruptures [20]. The sub-endothelium comes in contact with the blood and the clotting cascade is activated. The resultant thrombosis may lead to total occlusion of the vessel. Another consequence of plaque rupture is the dispersal of its contents into the circulation, which may produce effects distant from the plaque but in the territory supplied by the affect vessel.

RISK FACTORS FOR ATHEROSCLEROSIS[21]

A number of biochemical, physiological and environment risk factors have been identified that modify atherogenesis.

I Modifiable risk factors

- Elevated serum lipid levels
- Cigarette smoking and exposure to tobacco smoke
- High blood pressure
- Diabetes mellitus
- Obesity
- Diet rich in saturated fats, cholesterol and calories

II Non modifiable risk factors

- Male gender
- Aging
- Family history of premature atherosclerosis
- Genetic abnormalities.

III Other risk factors (genetically determined)

- Hyperhomocysteinemia
- Lipoprotein (a)
- Fibrinogen
- Cytokines
- Thrombin

MANAGEMENT OF ATHEROSCLEROSIS

The dietary changes should take place to initiate cholesterol concentration lowering.

1. Decrease in food consumption to lower total calories in obese patients.
2. Reduction in the consumption of cholesterol containing foods
3. Decrease in saturated food intake and increase polyunsaturated fats.

Many research works say that the possible mechanism by which the unsaturated fats (as in corn oil) lower serum cholesterol level is by inducing the excretion of cholesterol, cholesteryl esters and bile acids. Also some studies say the effect of corn oil may also be due to the presence of plant sterols like β-sitosterol. Unsaturated fatty acids occupy greater area than saturated fatty acids thereby altering the spatial configuration of the lipoprotein into which they are incorporated as a result fewer unsaturated lipid molecules can be accommodated by the protein portion of the lipoprotein and hypolipidemic effect is observed. The cholesterol lowering effect of unsaturated fatty acids is associated with decrease in both LDL and HDL cholesterol, also a reduction in HDL_2 to HDL_3 ratio, which might be undesirable.

Some forms of hyperlipidemia can be controlled by carbohydrate restriction. In early 1939, Burger observed an increase in serum cholesteryl esters following glucose, starch, sucrose and fructose ingestion. When carbohydrate is substituted for dietary fat, marked increase of triglyceride levels is

observed. A disturbance in carbohydrate metabolism can be responsible for atherosclerosis and thus carbohydrate be included in the list of primary risk factors. Non-drug therapy is done by bringing about a change in the life style of the persons who are likely to suffer from this disease or those who are been diagnosed as patients. The development of atherosclerosis may be due to diabetes mellitus, hypothyroidism, hypertension, which should be treated to reduce the risk of hypercholesterolaemia.

(ii) Drug therapy

There are five classes of drugs which reduce the lipid levels in the blood. Based on the types of drug and their main modes of action they have been broadly classified in to seven sections for convenience and these are given below.

- Cholesterol biosynthesis inhibitors (HMG-CoA reductase inhibitors)
- Fibrates
- Bile acid sequestrant resins
- Cholesterol absorption inhibitors
- LDL oxidation inhibitors
- Unique hypolipidemic drugs with multiple modes of action
- Recent approaches

(a) Cholesterol biosynthesis inhibitors (HMG-CoA reductase inhibitors)[22]

Statins, now the first-line agents for efficacious lipid-lowering therapy, primarily target reduction of elevated levels of atherogenic apoB-containing lipoproteins, and notably LDL, but equally lower plasma concentrations of VLDL, their remnants and IDL[23]. Thus, statins directly inhibit cholesterol synthesis (primarily in the liver) by blocking HMG-CoA reductase, the principal rate-limiting enzyme of cholesterologenesis that transforms HMG-CoA to mevalonic acid. Decreased endogenous cholesterol synthesis leads to reduction in the hepatic cholesterol pool and upregulates expression of hepatic LDL receptors. In this way, plasma LDL clearance is increased with reduction in the number of circulating LDL particles [24, 25]. The indirect reduction of endogenous CETP activity is an integral feature of the HDL-raising action of statins.

(b) Fibric acid derivatives

Clofibrate Gemfibrozil, Fenofibrate, Ciprofibrate. These compounds act by increasing the activity of lipoprotein lipase, an enzyme which promotes the catabolism of VLDL and LDL, clofibrate inhibits the hepatic synthesis of triglycerides leading to lower output of triglycerides by increasing the rate of synthesis of Hepatic mitochondrial α-glycerol phosphate dehydrogenase resulting in reduced availability of precursor α-glycerophosphate for the synthesis of triglycerides in the liver. It also inhibits cholesterol biosynthesis by competitive inhibition of HMG-COA reductase.

(c) Bile acid binding resins

Cholestyramine and colestipol[26.] These resins are not absorbed when given orally. They bind bile acid in the intestine and increase the faecal excretion of bile acids which necessitates liver to synthesis more and more bile acids. This results in the increased utilization of cholesterol for bile acids synthesis and its elimination.

(d) Cholesterol absorption inhibitors

An approach that has received intensive research attention in recent years is inhibition of Acyl Coenzyme A Cholesterol Acyl Transferase (ACAT) is an enzyme that esterifies cholesterol in the body by a process believed to be a key step for cholesterol absorption. ACAT inhibitors also have potential actions beyond inhibition of cholesterol absorption. Inhibition of hepatic ACAT could reduce the production of cholesteryl esters for packaging in lipoprotins, whole inhibition of ACAT at the artery wall could reduce the deposition of cholesteryl esters in atherosclerotic lesions. Several potent ACAT inhibitors have been reported in recent years.

(e) LDL oxidation inhibitors

Probucol is a synthetic lipophilic antioxidant. It acts by preventing the oxidation of LDL. It is believed that LDL has to undergo oxidation before depositing its cholesterol content in the artery wall.

(f) Unique hypolipidemic drug with multiple modes of action

In this group there are four drug groups which warrant special mention; (i) Nicotinic acid (ii) Gugulipid (iii) Compound 80/574 (iv) Natural sources and phytochemical.

(i) Nicotinic acid

It reduce lipolysis in adipose tissues, direct inhibition of the synthesis and secretion apoB containing particles by the liver, a reduction in the synthesis of lipoprotein (a) [LP(a)] and changes in the metabolism of the HDL particles with a resultant shift in HDL subtype distribution. Triglycerides, cholesterol are decreased, VLDL, LDL production falls and HDL increases.

(ii) Gugulipid

Gugulipid is a plant sterol and steroid derived from *Commiphora mukul*. Gugulipid exerts hypolipidemic effects by inhibition of cholesterol biosynthesis, enhancing the rate of excretion of cholesterol, promoting rapid degradation of cholesterol, thyroid stimulation, alterations in biogenic amines.

(iii) Natural Sources and Phytochemicals

Costal Eskimos eat a traditional diet rich in fish and seeds are known to have a low incidence of cardiovascular diseases. This is believed to be due to consumption of fish rich in the ω-3 fatty acids namely eicospentanoic acid and docosahexanoic acid. ω-3 fatty acid rich fish oil also reduces blood cholesterol.

CONCLUSION

In conclusion, there is abundant evidence today from observational, experimental and epidemiological studies that novel risk factors of atherosclerosis exist which exerts their effects on the arteries either in combination with or above and beyond the classical risk factors. However, there are limited data to suggest that interventions aiming at modification of the novel risk factors reduce CVD morbidity and mortality and further prospective studies are needed to address this issue.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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