The Role of Lipids in Atherogenesis

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INTISARI

Ahmad H. Asfie & R.M. Saradjja – Peran lipid dalam atherogenesis


Disisi pada bahwa kalsium lipid yang berupa peningkatan kolesterol (HDL) dan trigliserida (VLDL, terutama VLDL-istk), dan penurunan HDL, merupakan faktor risiko berat atherosklerosis. Faktor hormon balai berperan dalam proses atherogenesis, dan diselip melalui asam homoserine metabolisme lipid.

KeyWords : atherosclerosis – lipid – lipoprotein – splaniprotein – coronary heart disease

INTRODUCTION

High plasma cholesterol levels, hypertension, diabetes mellitus and smoking have long been known as risk factors for premature coronary artery disease. There is tremendous interest in the role of lipids in the evolution of atherosclerosis. Lipid

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Research Clinics Coronary Primary Prevention Trial (LRCP, 1984a, b) is a classic study demonstrating that reduction in plasma cholesterol, especially low density lipoprotein (LDL) cholesterol, decreases the risk of coronary artery disease. Premature atherosclerosis is often associated with lipoprotein abnormalities. In both cross sectional and longitudinal population studies, lipoprotein abnormalities are highly predictive to the development of coronary atherosclerosis and as such are considered among the major risk factors. The prominent alterations that are consistently related to atherogenesis, whether directly or indirectly, include hypercholesterolemia reflecting increased levels of LDL (Mason et al., 1986), hypertriglyceridemia reflecting increased concentration of VLDL (very low density lipoprotein) and/or remnants and triglyceride enrichment of LDL and HDL (high density lipoprotein) (Austen, 1989), increased apo-B levels (Brunzell et al., 1984), and reduced levels of HDL, particularly HDL2 particle subtraction and its major apolipoprotein, apo A-I (Moriécs et al., 1983). Evidence from controlled clinical trials has clearly established the benefits of lowering cholesterol either by diet or a combination of diet and hypolipidemic drug therapy (Blackschmer et al., 1987; Brennike et al., 1984; Frick et al., 1987; LRCP, 1984a, b).

Hyperlipidemia consists of excessive accumulation of one or more major lipids transported in plasma and is a manifestation of one or more abnormalities of lipid metabolism or transport (Bierman & Glomset, 1992).

According to current concepts of atherogenesis (Ross, 1986; Steinberg, 1983) cholesterol-rich and triglyceride-rich lipoproteins may play a direct role in lesion formation. Both arterial endothelial cells and smooth muscle cells take up LDL cholesterol and remnant cholesterol via both the cellular LDL receptor-mediated and receptor-independent pathways (Chai et al., 1988).

By 1986 over 270 coronary heart disease (CHD) risk factors had been reported (Hopkins & Williams, 1986). These include premature grey hair, premature baldness, snoring, a wife’s love, and meteorologic changes (Gould et al., 1978; Konkroko, et al., 1987).

This article reviews the role of lipids in atherogenesis. Which lipoproteins are atherogenic?

**DISCUSSION**

**Normal lipoprotein metabolism**

Lipoproteins are spherical macromolecular complexes consisting of an outer water soluble coat containing a lipids and apoproteins or apolipoproteins, phospholipid, etc. free cholesterol enveloping an inner core of the so-called "neutral" lipid composed of triglycerides and cholesterol esters (Ginsberg, 1990). The lipid moieties are either acquired from the diet or synthesized by the body, principally by the liver and small intestine. The apolipoproteins are also synthesized by these organs.

Lipoproteins are divided into seven classes which have been defined by their physico-chemical characteristics. These include chylomicrons, VLDL, intermediate-density lipoproteins (IDL), LDL, and HDL. The physico-chemical characteristics of the major lipoprotein classes are presented in TABLE I.
All lipoproteins have the same basic structure, but differ in relative amount of basic ingredients. Chylomicrons and VLDL carry mostly triglyceride and are large particles, with a substantial core and a thin shell. HDL has a thick shell of protein and phospholipid but carries relatively little cholesterol and triglyceride. LDL carries about 70 to 80% of the serum cholesterol.

The functions of lipoprotein in large part are to transport particles, delivering lipid to cells for energy (triglyceride) or as precursor (cholesterol) for the synthesis of cell membranes, bile acids, and both the adrenal and gonadal steroids. To accomplish these functions lipoproteins undergo a highly complex series of reactions that occur both within the vascular compartment and intracellularly. Exchange of both apoproteins and lipid moieties occurs constantly among lipoproteins in the circulation. Therefore, the composition and size of lipoprotein particle are constantly changing. Core components and components of the surface layers are constantly moving from particle to particle and this occurs both within and between lipoprotein layers. In reality, the lipoproteins are dispersed along a continuum of densities and sizes. As a result, the concept of individual subclasses such as LDL and HDL is a simplistic view of the biologic situation and is mainly served to elucidate mechanisms of metabolism.

<table>
<thead>
<tr>
<th>Lipoproteins</th>
<th>Density (g/dl)</th>
<th>MW (Daltons)</th>
<th>Diameter (nm)</th>
<th>Lipid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>0.95</td>
<td>400,000*10^6</td>
<td>75-1200</td>
<td>80-95</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.90-1.006</td>
<td>40-400*10^6</td>
<td>50-40</td>
<td>55-80</td>
</tr>
<tr>
<td>IDL</td>
<td>1.006-1.019</td>
<td>5-10*10^6</td>
<td>25-55</td>
<td>20-50</td>
</tr>
<tr>
<td>LDL</td>
<td>1.019-1.063</td>
<td>2.3*10^6</td>
<td>18-25</td>
<td>5-17</td>
</tr>
<tr>
<td>HDL</td>
<td>1.063-1.210</td>
<td>1.7-3.6*10^6</td>
<td>5-12</td>
<td>5-10</td>
</tr>
</tbody>
</table>

*MW: molecular weight (Daltons), TG: triglyceride, CH: cholesterol, PL: phospholipid

Triglycerides

Triglycerides are the major lipids in chylomicron and VLDL and serve as energy substrates in the liver and peripheral tissues, particularly muscle. The triglyceride molecules are nonpolar and must be carried in the core of the lipoproteins. Triglycerides can be transferred between lipoproteins in association with the apoprotein, and cholesteryl ester transfer protein.

Cholesterol

Cholesterol is a major lipid in LDL and HDL. In lipoproteins, cholesterol is formed mainly as cholesteryl ester in the core of the lipoprotein particle. A small proportion of lipoprotein cholesterol is carried as free cholesterol in the bilayer surface of the lipoprotein particle. Cholesteryl esters containing long-chain saturated or unsaturated fatty acids are derived from the action of plasma enzyme lecithin:cholesterol acyltransferase (LCAT) and constitute the majority of cholesterol esters in lipoproteins. Cholesteryl acetate, a minor type of cholesteryl ester in lipoproteins, is the product of the intracellular enzyme acyl coenzyme A-cholesterol acyltransferase (ACAT).
Phospholipids

Phospholipids make up the vast majority of the surface of lipoproteins, forming bilayers that act as an interface with both the polar plasma components and the nonpolar lipids of the lipoprotein core. Phosphatidylcholine (lecithin) is the major phospholipid in plasma and is the source of lecithine for cholesteryl ester formation by the LCAT reaction.

Apolipoproteins

Apolipoproteins are surface proteins, of which many different types exist. Apolipoprotein families were originally named for the lipoprotein in which they were thought to be predominated. For example, apolipoprotein B-100 is found largely in LDL and is also called lipoprotein. Differences in function and metabolism of the lipoproteins are largely governed by the presence of apolipoproteins.

Apolipoprotein provide structural stability to the lipoproteins, whereas others act as biologic detergents to solubilize the otherwise insoluble lipids, thereby enabling their transport in the aqueous environment of the plasma. They also play as co-factors with various enzymes involved in lipid metabolism, activate various enzymes such as lipoprotein lipase (LPL) and lecithin-cholesterol acyltransferase (LCAT), and serve as recognition sites for receptors on the surface cells (apo B-100 acts as a binding protein cell receptor for LDL). There are 11 major apoproteins named alphabetically (TABLE 2).

### TABLE 2. Characteristics of the major apolipoproteins (Grunberg, 1990)

<table>
<thead>
<tr>
<th>Apoprotein</th>
<th>MW</th>
<th>Lipoproteins</th>
<th>Metabolic Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-1</td>
<td>28,016</td>
<td>HDL, chylomicrons</td>
<td>Structural component of HDL, LCAT activator</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td>17,014</td>
<td>HDL, chylomicrons</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td>46,485</td>
<td>HDL, chylomicrons</td>
<td>Unknown; possibly facilitates transfer of other apo's between HDL and chylomicrons</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td>400,000,000</td>
<td>Lipoprotein (LPL)</td>
<td>Chylomicrons</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>512,000</td>
<td>VLDDL, IDLI, LDL</td>
<td>Necessary for assembly and secretion of chylomicrons from the small intestine</td>
</tr>
<tr>
<td>Apo C-III</td>
<td>6,630</td>
<td>All major lipoproteins</td>
<td>Activity of lipoprotein lipase</td>
</tr>
<tr>
<td>Apo C-III</td>
<td>8,700</td>
<td>All major lipoproteins</td>
<td>Inhibitor of lipoprotein lipase; may inhibit uptake of chylomicrons and VLDL remnants by the liver</td>
</tr>
<tr>
<td>Apo D</td>
<td>22,000</td>
<td>Mainly HDL</td>
<td>Possibly involved in reverse cholesteryl transport</td>
</tr>
<tr>
<td>Apo E</td>
<td>34,145</td>
<td>All major lipoproteins</td>
<td>Ligan for binding of several lipoproteins to the LDL receptor and possibly to a separate hepatic apo E receptor</td>
</tr>
</tbody>
</table>

MW: molecular weight

Apo B-100 is the major apolipoprotein of VLDDL, IDL, and LDL, constituting approximately 30%, 60%, and 95% of the protein in these respective lipoproteins. Apo
B-100 is the largest apolipoprotein, and contains several domains that could serve as a binding site for the LDL receptor. Such domains are shown in apo B-48. Readers who are interested in further information about the physiology of lipoprotein should refer to a detailed review by Ginsberg (1990).

**VLDL, LDL, and HDL metabolism**

After being secreted by liver, the VLDLs acquire C apoproteins from HDLs. One of these (apo C-II) activates lipoprotein lipase attached to the capillary endothelium, which in turn hydrolyzes the triglyceride in the particles. The free fatty acids are then released into the tissue. As the particles become smaller, they become relatively thicker and relatively enriched with cholesterol ester-rich remnants which are partly cleared by the liver and partly converted to LDL. The LDL are removed from circulation by a receptor-mediated process. Protein with a high affinity for the apo B of LDL have been demonstrated in many human cells. The binding of LDL to a receptor leads to endocytosis of the particle and its degradation. This process provides the cells with cholesterol for membrane synthesis, but the amount delivered is in excess of the requirement. Removal of the surplus seems to be a function of HDL. These particles are probably secreted by the liver and small intestine and contain activator, apo A-I, of lecithin-cholesterol acyltransferase (LCAT). Once cholesterol molecule has moved to HDL, it is transferred by LCAT. In this form it cannot return to the cell, but enters the core of the particle or is transferred to VLDL by a transfer protein. Thus, during lipoprotein metabolism, LDL continuously delivers cholesterol to cells, while HDL continuously removes it.

**Atherosclerosis**

Atherosclerosis is a vascular disease primarily affecting large and medium size arteries. In its most advanced form, it presents as a complex lesion consisting of proliferating smooth muscle cells, with macrophage monocytes invading fibroblasts and transforming to foam cells, followed by lipid deposition, fibrosis and calcification.

Epidemiological studies have clearly shown that hypertension, hypercholesterolemia, diabetes and smoking increase the possibility of atherosclerosis. The association of these risk factors with cholesterol has been well documented, by which, cholesterol elevation plays a significant role in the pathogenesis of atherosclerosis (Custer et al., 1956; Gudni et al., 1977; Kannel et al., 1979; LRCP, 1984a, b, Coronary Drug Project Research Group, 1975).

The initial step in the atherosclerosis process is believed to be endothelial dysfunction. Once it occurs, the production of endothelium-derived relaxant factor (EDRF), prostacyclin and other important tone and cellular proliferation regulators becomes less effective. Therefore, the chances for smooth muscle cells to migrate and proliferate in the subintimal area increase. In addition, endothelial dysfunction can lead monocyte adhesion and platelet adhesion and activation. Upon penetrating the vessel wall, the monocyte becomes macrophage and LDL cholesterol becomes oxidized (Dinarel, 1990).

The association between total plasma cholesterol levels with incidence of coronary heart disease is well established (LRCP, 1984a, b). The major components of
atherosclerotic plaque which are ultimately responsible for clinical effects, are deposited as lipids, mostly cholesteryl ester and cholesterol, and proliferated, modified arterial smooth muscle cells with their synthesized connective tissue products. Deposited cholesteryl ester and cholesteryl are derived largely from the lower density lipoprotein of the blood. The proportion of advanced plaques varies widely. However, evidence indicates that lipid deposition, especially lipoprotein elements, often occurs in the lesion-prone initial areas of the athero prior to the build of smooth muscle cells. Excessive accumulation of cholesterol (or cholesteryl ester) leads to foam cell formation and fatty plaques. Elevated LDL may also damage endothelial cells and stimulate the proliferation of arterial smooth muscle cells (Hender et al., 1983). Cholesterol-rich and LDL remnants, cholesterol-rich B-VLDL produced by high cholesterol intake and altered LDL can also be taken by monocyte-derived macrophages which enter the arterial wall during atherogenesis (Brown & Goldstein, 1983).

Before LDL can be incorporated into foam cells of atheroma, it must be modified within the arterial wall. Habelle et al. (1988) and Steinberg et al. (1999) repeated that modified LDL increases its atherogenicity. Possible modifications are oxidative (Steinberg et al., 1989), derived formation (Fugelso et al., 1985), and self-aggregation (Khos et al., 1990). Oxidatively modified LDL can contribute to the atherosclerotic process through 4 mechanisms (Steinberg, et al., 1989). Firstly, the oxidized LDL is recognized by the scavenger receptor of the macrophage, thus contributing to the foam cell lesion development. The scavenger receptors only recognize modified LDL. Although the precise mechanisms are unknown, these cells are able to generate active oxygen species, which can induce lipid peroxidation and lead to breakdown of lipoprotein B. Secondly, oxidized LDL is chemotactic for blood monocytes, thereby augmenting their recruitment to the arterial intima. Thirdly, oxidized LDL is cytotoxic to cells within arterial wall (Hender et al., 1983; Mord et al., 1984), and provides a potential mechanism for cellular necrosis and perhaps endothelial injury which may facilitate the process of brumegogenesis. Finally, oxidized LDL appears to function as a migration inhibiting factor, prolonging the residence time of the macrophages within the arterial intima. Thus, oxidized LDL may contribute to the loss of endothelial cells and promote infiltration of lipoproteins and circulating monocytes and platelets, setting the stage for the evolution of the advanced atherosclerotic plaque.

Although the cause and effect relationship between hypercholesterolemia and atherosclerosis has been well established, the potential associations between elevated triglyceride or decreased high-density lipoprotein levels and atherosclerosis remains controversial. The National Cholesterol Education Program (1988) did not list them as cardiovascular risk factors. In contrast, the European classification of hyperlipidemia states that hypertriglyceridemia is an important cholesterol risk factor. Currently, attention (European Atherosclerosis Society, 1988). Recently, an international committee summarized the findings on hypertriglyceridemia as a risk factor for cardiovascular disease (Aarsman et al., 1991). The findings of the Framingham Heart Study show that triglycerides are independent coronary artery disease risk factors. The Framingham Heart Study showed that triglycerides are independent coronary artery disease risk factors. Therefore, elevated VLDL level results in hypertriglyceridemia and may also cause coronary artery disease. Most studies indicate that the elevation of VLDL alone is not an independent coronary artery disease risk factor (Halley et al., 1980). Therefore,
hypertriglyceridemia with modest elevation of serum cholesterol due to the elevation of VLDL levels does not warrant any treatment. However, elevated VLDDL levels are often found in individuals who are at increased coronary risk on the basis of other associated factors, such as obesity, hypertension, glucose intolerance, and low HDLC levels. Results from the Framingham Heart Study (Castelli, 1986) strongly suggest that high triglyceride levels are "independent" risk factors for coronary heart disease.

Most fasting triglycerides circulate with VLDDL and several lines of data suggest that some VLDDL particles, particularly VLDDL remnants, are atherogenic (Grundy, 1990). Moreover, elevated triglyceride level is associated with small, dense LDL particle and low levels of HDLC both of which seem to increase the risk coronary heart disease.

Kannel et al. (1979) reported that low serum HDLC cholesterol level is the strongest single lipid predictor of coronary heart disease. Several risk factors for coronary heart disease, such as smoking, obesity, dietary life, lower HDLC-cholesterol levels. If these are present, a low serum HDLC may be associated with coronary heart disease without necessarily being a cause of coronary heart disease. HDLC cholesterol concentration is inversely correlated with those of VLDDL and LDL, which is known to be atherogenic.

A variety of hormones and other circulating cell deriving growth factors may also contribute to atherogenesis. Insulin resistance, hyperinsulinemia, insulin-like growth factor 1 (IGF-1, also called somatomedin-C), and platelet-derived growth factors (PDGF) can stimulate arterial smooth muscle cell proliferation. This mitogen also flux of LDL into cells by increasing the LDL receptor level and promoting cholesterol biosynthesis intracellularly (Stout, 1982). On the other hand, insulin deficiency (and thyroid hormone deficiency) may influence atherogenesis via impaired LDL-receptor mediated catabolism, resulting in high circulating LDL and VLDDL remnant levels. Glucocorticoids, progestogens, and estrogens may influence lipoprotein concentration and composition and directly affect arterial cell function (Bierman & Glomset, 1992).

CONCLUSION

A short review on the role of lipid in atherogenesis has been discussed. Accumulation of lipids in the intima of arteries increased with age. High cholesterol and triglyceride levels increased the risk of atherogenesis. It has been proposed that LDL may become very atherogenic if it undergoes a cell-mediated oxidative modification within arterial wall to a form recognizable by scavenger receptor on macrophage contributing to foam cell and lesion development. Oxidized LDL is chemoattractant for blood monocytes, cytotoxic to cells within the arterial wall, and inhibits cholestasis of macrophages thereby prolongs the resident time of macrophages within the arterial intima. These mechanisms are proposed to be responsible for atherogenesis through their effects on lipid metabolism. Lowering cholesterol levels and preventing this oxidative modification may retard the development of the atherosclerotic process.

REFERENCES
