Berkala Ilmu Kedokteran
Jil. XXVI, No. 2, Juni 1994

The Role of Lipids in Atherogenesis[1]

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INTISARI

Ahmad H. Asdie & R.M. Sarodja – *Peran lipid dalam aterogenesis*

Hiperkolesterolemia, hipertensi, diabetes dan merokok telah lama diakui sebagai faktor risiko utama penyakit jantung koroner. Komponen utama bercak aterosklerotik adalah timbunan lipid, terutama ester kolesterol dan kolesterol, proliferasi dan perubahan sel otot polos intima arteri. Timbunan lipid dalam intima arteri terutama berasal dari *low-density lipoprotein* (LDL) yang telah termodifikasi dalam darah. Hal ini terjadi sebelum proliferasi otot polos intima timbul. Walaupun hubungan kausal antara hiperkolesterolemia dan penyakit jantung koroner sudah lama diterima para pakar, namun mengenai peran trigliserida dan jenis lipoprotein lainnya (*high density lipoprotein*, HDL) masih belum didapatkan kesepakatan. Dalam makalah ini dibahas peran lipid dalam proses aterogenesis.

Disimpulkan bahwa kelainan lipid yang berupa peninggian kolesterol (dan LDL) dan trigliserida (VLDL, terutama VLDL-sisa), dan penurunan HDL merupakan faktor risiko bebas aterogenesis. Faktor hormonal ikut berperan dalam proses aterogenesis, dan diduga melalui efek hormon terhadap metabolisme lipid.

Key Words : atherosclerosis – lipid – lipoprotein – apolipoprotein – 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

1 Partly presented at the Scientific Meeting on Prevention and Treatment of Cardiovascular Risk, Department of Medicine, Faculty of Medicine, Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, September 28, 1993.

0126-1312/94/2602-0105$01.00

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 (Martin *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) (Austin, 1989), increased apo-B levels (Brunzell *et al.*, 1984), and reduced levels of HDL, particularly HDL_2 particle subfraction and its major apolipoprotein, apo A-I (Maciejko *et al.*, 1983). Evidence from controlled clinical trials has clearly established the benefit of lowering cholesterol either by diet or a combination of diet and hypolipidemic drug therapy (Blankenhorn *et al.*, 1987; Brensike *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 (Chait *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 (Gouid *et al.*, 1978; Koskenvuo, *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 protein called apoprotein or apolipoprotein, phospholipid, and 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 several classes which have been defined by their physico-chemical characteristics. These incude chylomicrons, VLDL, intermediate-density lipoproteins (IDL), LDL, and HDL. The physico-chemical characteristics of the major lipoprotein classes are presented in TABLE 1.

All lipoproteins have the same basic structure, but differ in relative amount of basic ingredient. 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 apoprotein and lipid moieties occurs constantly among lipoproteins in the circulation. Therefore, the composition and size of lipoprotein particle are constantly changed. 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 mechanism of metabolism.

TABLE 1. – Physico-chemical characteristics of the major lipoprotein classes

Lipoproteins	Density (g/dl)	MW (Daltons)	Diameter (nm)	Lipid (%)		
				TG	CH	PL
Chylomicrons	0.95	$400x10^6$	75-1200	80-95	2-7	3-9
VLDL	0.950-1.006	$10-80x10^6$	30-80	55-80	5-15	10-20
IDL	1.006-1.019	$5-10x10^6$	25-35	20-50	20-40	15-25
LDL	1.019-1.063	$2.3x10^6$	18-25	5-15	40-50	20-25
HDL	1.063-1.210	$1.7-3.6x10^6$	5-12	5-10	15-25	20-30

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 carrier protein, and cholesteryl ester transfer protein.

Cholesterol

Cholesterol is a major lipid in LDL and HDL. In lipoproteins, cholesterol is formed mainly as cholesterol 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 linoleate are derived from the action of plasma enzyme lecithin-cholesterol acyltransferase (LCAT) and constitute the majority of cholesterol esters in lipoproteins. Cholesteryl oleate, a minor type of cholesterol ester in lipoproteins, is the product of the intracellular enzyme acyl coenzyme A-O-acyl-transferase (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. Phosphotidyl-choline (lecithin) is the major phospholipid in plasma and is the source of linoleate 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.

Apolipoproteins 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 palsma. 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 (Ginsberg, 1990)

Apoproteins	MW	Lipoproteins	Metabolic Functions
Apo A-I	28,016	HDL, chylomicrons	Structural component of HDL, LCAT activator
Apo A-II	17,414	HDL, chylomicrons	Unknown
Apo A-IV	46,465	HDL, chylomicrons	Unknown: possibly facilitates transfer of other apos between HDL and chylomicron
Apo (a)	400-800,000	Lipoprotein (a)	
Apo B-48	264,000	Chylomicrons	Necessary for assembly and secretion of chylomicrons from the small intestine
Apo B-100	512,000	VLDL, IDL, LDL	Necessary for assembly and secretion of VLDL from the liver; structural protein of VLDL, IDL, LDL, ligand for LDL receptor
Apo C-I	6,630	All major lipoprotein	
Apo C-II	8,900	All major lipoprotein	Activator of lipoprotein lipase
Apo C-III	8,800	All major lipoprotein	Inhibitor of lipoprotein lipase; may inhibit uptake of chylomicron and VLDL remnants by the liver
Apo D	22,000	Mainly HDL	Possibly involved in reverse cholesterol transport
Apo E	34,145	All major lipoproteins	Ligand for binding of several lipoproteins to the LDL receptor and possibly to a separate hepatic apo E receptor

MW : molecular weight

Apo B-100 is the major apolipoprotein of VLDL, 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 domain is absent from 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 hydrolyses the triglyceride in the particles. The free fatty acids are then released into the tissues. 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. Proteins 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, of lecithin–cholesterol acyltransferase (LCAT). Once cholesterol molecule has moved to HDL, it is esterified 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.

Atherogenesis

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 (Canner *et al.*, 1986; Gordon, *et al.*, 1977; Kannel *et al.*, 1979; LRCP, 1984a, b; Coronary Drug Project Research Group, 1975).

The initial step in the atherogenesis process is believed to be endothelial dysfunction. Once it occurs, the production of endothelium derived relaxant factor (EDRF), prostacylclin 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 (Dzau, 1990).

The association between total plasma cholesterol level 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 esters and cholesterol 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 intimal areas of the artery prior to the build of smooth muscle cells. Excessive accumulation of cholesterol (as 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 (Hessler *et al.*, 1983). Chylomicrons and VLDL remnants, cholesterol-rich β-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 incorparated into foam cells of atheroma, it must be modified within the arterial wall. Haberland *et al.* (1988) and Steinberg *et al.* (1989) reported that modified LDL increase its atherogenicity. Possible modifications are oxidative (Steinberg *et al.*, 1989), derivated formation (Fogelman *et al.*, 1980), and self aggregation (Khoo *et al.*, 1990). Oxidatively modified LDL may contribute to the atherogenic 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 and 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 apolipoprotein B. *Secondly*, oxydized LDL is chemotactic for blood monocytes, thereby augmenting their recruitment to the arterial intima. *Thirdly*, oxidized LDL is cytotoxic to cells within arterial wall (Hessler *et al.*, 1983; Morel *et al.*, 1984), and provides a potential mechanism for cellular necrosis and perhaps endothelial injury which may facilitate the process of thrombogenesis. *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 association 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 stated that hypertriglyceridemia needs particular attention (European Atherosclerosis Society Study Group, 1988). Recently, an international committee summarized the findings on hypertriglyceridemia as a risk factor for cardiovascular disease (Assmann *et al.*, 1991). The experience of the PROCAM (Prospective Cardiovascular Muenster) study showed that there are significant associations between the incidence of atherosclerotic coronary artery disease and high-density lipoprotein and triglyceride. Hypertriglyceridemia is a powerful additional risk factor when coincides with ratio of plasma low-density lipoprotein to HDL cholesterol greater than five (Assmann & Schulte, 1992).

Elevation of VLDL level results in hypertriglyceridemia and may also cause moderate degree of hypercholesterolemia. Most studies indicate that the elevation of VLDL alone is not an independent coronary risk factor (Hulley *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 VLDL 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 HDL 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 VLDL and several lines of data suggest that some VLDL particles, particularly VLDL remnants, are atherogenic (Grundy, 1990). Moreover, elevated triglyceride level is associated with small, dense LDL particle and low levels of HDLs, both of which seem to increase the risk coronary heart disease.

Kannel *et al.* (1979) reported that low serum HDL cholesterol level is the strongest single lipid predictor of coronary heart disease. Several risk factors for coronary heart disease, such as smoking, obesity, sedentary life, lower HDL-cholesterol levels. If these are present, a low serum HDL may be associated with coronary heart disease without necessarily being a cause of coronary heart disease. HDL cholesterol concentration is inversely correlated with those of VLDL 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 VLDL remnant levels. Glucocorticoids, progestogens, and estrogens may influence lipoprotein concentration and composition and directly effect 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 atherosclerosis. 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 scavanger receptor on macrophage contributing to foam cell and lesion development. Oxidized LDL is chemotactic for blood monocytes, cytotoxic to cells within the arterial wall, and inhibits chemotaxis of macrophages therefore it prolongs the residence time of macrophages within the arterial intima. These mechanisms are proposed to be responsible for atherogenesis through their effects on lipid metabolisms. Lowering cholesterol levels and preventing this oxidative modi- fication may retard the development of the atherosclerosis process.

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