Plasma Lipoproteins and Coronary Heart Disease

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Coronary heart disease (CHD) is a major cause of morbidity and mortality. High levels of some lipoproteins predispose to atherogenesis and CHD. The role of plasma lipoproteins in CHD is summarized in this paper. [Journal of Turgut Özal Medical Center 1997;4(3):312-318]

Key Words: *CHD, Lp(a), LDL, HDL, chylomicron, VLDL*

Plazma lipoproteinleri ve koroner kalp hastalığı

Koroner kalp hastalığı morbidite ve mortalitenin önemli bir sebebidir. Bazı lipoprotein düzeylerinin yüksekliği bunu hazırlayıcı sebeplerdendir. Bu makalede plazma lipoproteinlerinin koroner kalp hastalıklarındaki rolü özetlenmiştir. [Turgut Özal Tıp Merkezi Dergisi 1997;4(3):312-318]

Anahtar Kelimeler: *Koroner kalp hastalıkları, Lp(a), LDL, HDL, şilomikron, VLDL*

Coronary heart disease (CHD) is a major cause of morbidity and mortality (1). Synonyms for CHD include ischemic heart disease (IHD) (2), coronary artery disease (CAD) (1) and atherosclerotic coronary vascular disease (ASCVD) (3). Although the exact etiology is unknown, a large number of risk factors are known to be associated with CHD. These include obesity (4,5), diabetes mellitus (6,7), hypertension (8), smoking (9-11), age and sex (12), family history (13), plasma lipoprotein abnormalities (14-16), abnormalities in coagulation proteins (17-19), serum bilirubin (20-22), homocysteine (23,24), and cardiac troponin T (25). Although each of these factors play role in the pathogenesis of atherosclerosis, recent studies have shown that plasma lipoprotein abnormalities may play a dominant role in influencing atherosclerotic lesions in CHD. Several lipoproteins have been identified in plasma and include lipoprotein (a) [Lp(a)](26), low density lipoproteins (LDL), high density lipoproteins (HDL) chylomicrons, and very low density lipoproteins (VLDL) (27). The object of this paper is to summarize the role of plasma lipoproteins in CHD.

Lipoprotein (a) [Lp(a)]: Lp(a) particles are heterogenous in density and size, and consist of approximately one third phospholipids, one third cholesterol, and one third protein (28). The protein of Lp(a) is comprised of apo B-100 linked by disulfide bridge to apo A. Apo A, a unique protein, is glycosylated and the molecular weight varies from 300,000 to 800,000 daltons. Heterogeneity is due to the polypeptide chain polymorphism and the extent of glycosilation. When exposed to a sulfhydryl reducing agent, apo A can be removed from Lp(a) by ultracentrifugation resulting in free apo A and Lp (a-) particles. Lp (a-) is somewhat larger than LDL and contains more triglyceride and is covered completely by apo B-100 (29). Plasma levels of Lp(a) are genetically controlled. The distribution of Lp(a) level

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in population is profoundly skewed (30). The apo A gene is located on the long arm of chromosome 6 q (26-27) and is closely linked to the plasminogen gene (29).

Lp(a) is synthesized in liver (29-31), however apo A mRNA has also been identified in brain and testes (32). After synthesis, the apo A is covalently linked to Lp(a) and other plasma lipoproteins (29). Lp(a) inhibits 3-hydroxy 3-methylglutaryl coenzyme A reductase suggesting uptake of Lp(a) into the cells. Intracellular release of cholesterol, from Lp(a) thus helps to regulate de novo cholesterol synthesis (33).

Lp(a) is removed from plasma by similar mechanisms as LDL, but less efficiently. Lp(a) may be preferentially removed by the scavenger pathway (29) and therefore, like LDL contribute to foam cell formation. Lp(a) is less efficiently cleared by the liver than LDL. Familial hypercholesterolemia in apo A phenotypes synergistically elevates plasma Lp(a) levels (29,34). Lp(a) may facilitate atherogenesis by endothelial cell uptake. Lp(a) particles move to subendothelial space, interact with matrix constituents, undergo chemical modification and serve as ligand for scavenger uptake by foam cells (35,36).

Lp(a) and atherogenesis: Endothelial cell injury leads to the deposition of lipids in the subendothelium. Lp(a) and LDL are taken up by macrophages, resulting in formation of foam cells. At the same time endothelial injury leads to the deposition of platelets and fibrin in the subendothelium. These events stimulate smooth muscle proliferation and formation of atheromatous plaques (37). Although both Lp(a) and LDL are found in plaques, Lp(a) is preferentially deposited because Lp(a) bind more avidly to matrix constituents such as fibrin, glycosoaminoglycan, and fibronectin (38,39). Cholesterol loading of macrophages also enhances Lp(a) uptake and further induces foam cell formation (37,40). Lp(a) promotes smooth muscle proliferation by inhibiting transforming growth factor ß which is an inhibitor of smooth muscle growth (37).

Fibrinolytic system and Lp(a): In the fibrinolytic system, the inactive precursor plasminogen is activated to plasmin by tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Plasminogen activation is regulated by specific molecular interactions between t-PA, plasminogen and fibrin. Lysine binding sites anchor plasminogen on fibrin where activation to plasmin by t-PA occurs. Plasmin then degrades fibrin leading to clot lysis (41). Lp(a), like plasminogen, possesses several kringles containing lysine binding structures (42-44) and competitively inhibits the plasminogen fibrin interaction (19). Lp(a) has also been reported to inhibit the activity of t-PA as well as the thrombolytic activity of streptokinase. High levels of Lp(a) are reported to decrease plasmin, generation and decrease euglobulin clot lysis time (45). This impairment of fibrinolytic system may result in arterial thrombosis and atherosclerosis (46).

Lp(a) and risk of CHD: The Gottingen Risk Incidence and Prevalence Studies (GRIPS) ranked Lp(a) as an important risk factor for CHD. Elevated Lp(a) is particularly important in subjects with borderline LDL-C, since their risk for CHD increases from below average to above average if Lp(a) concentrations are >30 mg/dl. High concentrations of Lp(a) are also associated with increased risk of CHD even with LDL-C levels <150 mg/dl (<3.9 mmol/L). Increased Lp(a) concentrations as risk for CHD rank comparable to some of other risk factors including positive family history, low HDL-cholesterol (HDL-C) and hyperfibrinogenemia (15).

Lp(a) levels are twice as high as in acute unstable angina than in chronic stable angina (47). Age is weakly corelated with Lp(a) levels in women (48). Postmenopausal women tend to have higher Lp(a) levels than premenopausal women (12). The incidence of CHD is also higher in postmenopausal women (49). It is not certain whether the two are causally related (29). Available data suggest that both estrogen and progestrone regulate lipoprotein metabolism at different sites (50).

There are racial differences in Lp(a) levels. In blacks the Lp(a) levels are twice as high as in whites (48). In Chinese population lower molecular weight apo A isoforms are associated with high plasma Lp(a) levels and an increased risk of CHD (51). There does not appear to be a significant difference in Lp(a) levels in noninsulin dependent diabetic patients (NIDDM) and control subjects. In a subset of insulin dependent diabetics with microalbuminuria, Lp(a) levels are high. Overall there is little evidence that Lp(a) levels are associated with increased risk of CHD in diabetic patients (6). Authorities also disagree whether Lp(a) levels are an independent risk factor in increased incidence of CHD in familial hypercholesterolemia (52,53).

Low Density Lipoproteins (LDL): Plasma lipoproteins separate into 4 major fractions on agarose gel electrophoresis:1) Chylomicrons, 2) Very low density lipoproteins (VLDL), 3) Low density lipoproteins (LDL), 4) High density lipoproteins (HDL) (54). LDL contains mostly cholesterol (LDL-C) and 18-22 % protein which is predominantly apo B-100 and trace levels of apo E (55). Most LDL is derived from VLDL although there is evidence of de novo production in the liver (27).

LDL and atherosclerosis: Several steps have been postulated in formation of atherosclerotic plaque: 1) Increased transport of LDL in plasma in form of liposomes. During this transport LDL permeates into the arterial wall, is oxidized (Ox-LDL) and glycated. This leads to free radical formation, injury to overlying endothelium and adjascent smooth muscle cells. LDL is unlikely to get oxidized in circulation due to presence of antioxidants and metal ion chelator proteins. 2) Ox-LDL stimulates formation of monocyte binding molecules, monocyte chemotactic protein-1 (MCP-1) and macrophage colony stimulating factor (M-CSF). These cause entry and maturation of monocytes which engulf LDL and form foam cells. 3) Monocytes continue to enter the vessel at the edge of the lesion. 4) Ox-LDL leads to death of foam cells and forms a necrotic core. 5) Ox-LDL stimulates endothelium to produce tissue factor and accelerates platelet aggregation, thus promoting clot formation. 6) Some oxysterols stimulate calcification of the plaque. Plaque may rupture at the edge of the lesion, further promoting clot formation (46).

LDL and risk of CHD: Most authorities rank LDL-C as the strongest predictor of CHD and more important than positive family history, hyperfibrinogenemia and low HDL. According to GRIPS data, LDL-C levels of 190 mg/dl (4.9 mmol/L) or higher were associated with high incidence of CHD. Lp(a) is reported to potentiate LDL-C induced risk of CHD (15).

LDL-C is reported to be higher in menopausal women than premenopausal women and age matched men (50,56). This is probably related to estrogen loss following ovarian involution. It is interesting to note that levels of HDL do not decrease in these women suggesting no effect of hypoestrogenism on HDL (14). It also suggests that LDL-C is a risk factor independent of HDL (56). LDL-C shows no significant differences between blacks and whites (57).

High Density Lipoprotein (HDL): HDL contains 16-25 % cholesterol and cholesteryl ester and 45-55 % protein mainly apo A-I, apo A-II and apo D. HDL is mostly synthesized in liver and intestine. However intestinal HDL does not contain apo C and apo E which are synthesized in liver and added to intestinal HDL. Apo C and apo E are required for metabolism of chylomicrons and VLDL (27).

Nascent HDL consists of a discoid bilayer of apolipoprotein and free cholesterol. Enzyme lecithin cholesterol acyltransferase (LCAT) binds to the disc and converts surface phospholipid and free cholesterol to cholesteryl ester and lysolecithin. Lysolecithin is transfered to serum albumin. Thus HDL is involved in removal of unesterified cholesterol from lipoproteins and tissues (27). HDL lipoproteins are encoded by genes clustered on chromosome 11. Several disorders are associated with mutations of these lipoproteins, in particular apo A-I, apo A-IV, and apo C-III lead to defect in synthesis or the function of HDL and development of atherosclerosis. For example, apo A-I serves as a factor in enzyme LCAT which catalyzes the conversion of cholesterol to cholestryl ester, the form transported in the HDL particle. Some variants of apo A-I are inefficient in this function (58).

Authorities vary in attaching importance of HDL vs. LDL as a risk factor for CHD (14,59). However the ratio of LDL-C to HDL-C or total cholesterol to HDL-C is accepted as extremely important indicator of atherogenesis (14). A Framingham study by Castelli examined a large number of risk factors and concluded that nonfasting HDL cholesterol and total cholesterol are intimately related to CHD (60). Based on Framingham data, optimal levels of HDL should be greater than 52 mg/dl (61).

Numerous epidemiologic studies from North America and Europe have conclusively demonstrated that elevated levels of HDL protect against CHD, and abnormally low level increases the risk of CHD (1,14,62). Hypertriglyceridemia leads to enrichment of HDL which is remodeled to form smaller particles, probably enhancing catabolism (63). Low levels of HDL are commonly seen in diabetic patients (NIDDM) and may contribute to higher risk of CHD (6). HDL levels increase with estrogen replacement therapy in postmenopausal women (64). HDL subfractions are increasingly recognized as an important factor associated with cardiovascular health. HDL2 had the strongest association with CHD (65),

even after controlling many demographic, historic, and medical risk factors (66).

Chylomicrons: Chylomicrons are very large spherical particles with a diameter 75-450 nm (67). They contain triglycerides (80-95%), phospholipids (3-7%), cholesteryl esters and unesterified cholesterol (3-7%), and protein (1-2%) (68). The proteins in chylomicrons are apo B-48, A-I, A-II, A-IV, C-I, C-II, and C-III. Only apo B-48 is required for chylomicron assembly (67). Molecular weight of chylomicrons vary from 0.4 to 30 kd (69). Chylomicrons are responsible for transporting dietary fat from the alimentary tract (54). They are synthesized and released from intestinal epithelium. Chylomicrons then make their way to lacteals draining the intestines (27) and then into lymphatics, thoracic duct and jugular vein and finally into systemic circulation (54). Chylomicrons are cleared rapidly from blood and within 1 hour, 80 % is found in adipose tissue, heart and muscle and 20 % in liver (27). As chylomicron circulates, triglyceride in its core is degraded by lipoprotein lipase. The particle size decreases but the density increases. These chylomicron remnants are removed by the liver cells by endocytosis. In the cell apolipoproteins, cholesteryl esters and other components are degraded, releasing aminoacids, free cholesterol and fatty acids. The released cholesterol regulates the rate of de novo cholesterol synthesis in liver by decreasing the cell content of HMG CoA reductase (70).

Chylomicrons and atherosclerosis: Disturbances in removal of postprandial chylomicrons from plasma exposes the vascular walls to these lipoproteins (71) suggesting direct involvement of these lipoproteins in pathogenesis of atherosclerosis (72). Normolipidemic patients with CHD are reported to have significantly higher levels of chylomicron remnants than normal subjects (73). Chylomicron remnants penetrate the arterial wall efficiently and are seletively retained at the site of lesion (74). Increased production of remnant particles by acyl-cholesterol acyltransferase (ACAT) may also be an important mechanism of the postprandial lipemia of CHD (71). Chylomicron remnants were found to be toxic to cultured smooth muscle cells (75) and macrophages (76). Thus damage to smooth muscles and macrophages in the arterial wall may be yet another mechanism by which chylomicrons can cause atherosclerosis (76).

Very low density lipoproteins (VLDL): VLDL is synthsized by the liver and intestines. The VLDL transports hepatic synthesized triglycerides and cholesterol. VLDL is about 30-80 nm in diameter and contains triglycerides (45-65%), phospholipids (15-20%), cholesterol esters and unesterified cholesterol (16-30%), and protein (6-10%) (68). Lipoproteins in VLDL are apo B-100, apo C, apo E and traces of apo A and B-48. The molecular weight is 5-10 kd (69). As VLDL passes through circulation, triglyceride is removed by lipoprotein lipase. Apo C and apo E are transfered to HDL. At the same time cholesterol esters are transfered from HDL to VLDL. This transfer is accomplished by cholesteryl ester transfer protein. The VLDL now contains equal amounts of cholesterol and triglycerides and is called intermediate density lipoprotein (IDL). IDL has a short life and is converted to LDL by liver (69).

VLDL and atherosclerosis: VLDL particles carry five times more cholesterol per particle than do LDL and are responsible for delivering substantial cholesterol to the arterial wall (7). Chylomicrons are too large to be able to penetrate arterial wall (72) but VLDL and chylomicron remnants with their small size may have greater propensity to traverse the arterial intima and induce foam cell formation (3). VLDL and chylomicrons are rich in triglycerides. Lipoprotein lipase avidly binds these triglyceride rich lipoproteins (TRL) to heparan sulfate which is abundant on the surface of many cells including macrophages found in arterial wall. This binding encourages cellular uptake of cholesteryl esters from TRL, thus providing another mechanism for atherogenity of TRL (77). Hypertriglyceridemia is positively associated with plasminogen activator inhibitor (PAI-1), a plasma protein which inhibits fibrinolysis (3) and may be partly responsible for CHD.

Conclusion: Lipoproteins play an important role in health and disease. Lipoproteins carry dietary lipids to the tissues to provide energy and fat storage. However abnormalities in lipoproteins are considered important risk factors in CHD. Endothelial injury can divert the normal transport of lipids from plasma to subendothelium. Here Lp(a) and LDL can stimulate the phagocytosis by macrophages, which are then transformed to foam cells. Lp(a) can also stimulate proliferation of smooth muscle cells. These events together with the deposition of fibrin and platelets and necrosis of subendothelial tissue lead to the formation of atheromatous plaques in coronary arteries, these plaque predispose to arterial thrombosis. Several studies have implied that high

levels of some of lipoproteins predispose to atherogenesis and CHD. They reported high incidence of atherosclerosis and CHD in subjects with Lp(a) levels above 30 mg/dl (15), LDL-C above 130 mg/dl (78), HDL below 35 mg/dl (69), and apo B above 1.2 mg/dl (52), cholesterol levels below 200 mg/dl (78,79) and triglyceride above 200 mg/dl (52). They conclude that levels of lipoprotein below the risk levels could decrease the risk of CHD considerably.

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