Editorial

Lipoprotein(a) and Diabetes

Lipoprotein(a) [Lp(a)] is emerging from an era of inattention to assume a possible leading role in degenerative disease. This low-density lipoprotein (LDL)-like particle is now both epidemiologically and mechanistically associated with coronary artery disease (1). Among nondiabetic non-black populations, it may be a potent marker and physiological element in the formation of atherosclerosis. Lp(a) may function in both the silent and climactic thrombotic events associated with intimal pathology, myocardial infarction, and stroke (2). Although it seems likely that Lp(a) will also be related to coronary vascular disease in diabetes, studies confirming this speculation are not available. Herein, we review the structure-function relationship of Lp(a) and the epidemiological evidence implicating its role in coronary disease and raise some questions regarding Lp(a) in diabetes.

WHAT IS Lp(a)?

Lp(a) is a complex particle containing lipid, protein, and carbohydrate. The protein core is composed of two large apolipoproteins (apo), apo(a) and B, linked together through a single disulfide bond (3). Cholesterol ester is the major lipid component, but it contains more triglyceride than LDL (4). Apo(a) mRNA is found in the liver, brain, and testes (5), but the particle's principal and possibly exclusive assembly point is the liver. Indirect evidence indicates that Lp(a) binds to the B-E receptor (6), but its intracellular metabolism may differ from LDL (7); much remains to be determined concerning the control of its production and clearance.

The distinguishing feature of Lp(a) and the focus of much scientific attention is its unique apo(a). Utermann et al. (8) found several isoforms of human apo(a) that vary extensively in both molecular weight (400,000–700,000 M_r) and carbohydrate content. There appears to be a direct relationship between the size of the phenotype expressed and the plasma concentrations; individuals expressing the larger apo(a) phenotypes are found to have the highest plasma concentrations of Lp(a) (9).

The most intriguing structural features of apo(a) are triple-loop cysteine-linked amino acid domains called kringles. These lysine-binding kringles get their name from the coiled fat-laden similarly atherogenic Danish pastry. Some of the kringles are strikingly similar to those in plasminogen (amino acid homology 75–94%), a serum proteolytic enzyme needed to promote the cleavage of clot-borne fibrin (10). The relationship between the two proteins is strengthened by the observation that the genes lie in close proximity to one another on the long arm of chromosome 6 (11). The structural similarity of the kringles to those in plasminogen casts suspicion that Lp(a) has a physiological or pathophysiological role in the clotting system. Therein may lie a key link between the lipoproteins and the final, often dramatic events in coronary heart disease.

Lp(a) may draw itself into thrombolysis through one or more mechanisms. It has been shown to reduce plasmin activity in vitro, although it has little or no plasminlike activity (12). Apo(a), probably through its lysine-binding kringles, adheres to fibronectin, complement C3, prothrombin (13), and, perhaps most importantly, fibrin (14). By binding to fibrin, it reduces the number of available sites to form a trimolecular complex composed of tissue plasminogen activator, plasminogen, and fibrin. This results in decreased production of plasmin and, consequently, reduced clot lysis.

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In vivo, Lp(a)'s role in atherosclerosis is one of guilt by association. The most concrete piece of evidence is the visualization of apo(a) immunoreactivity in human atheroma (15). It has been proposed that Lp(a) is drawn to nascent atheromata by fibrin surrounding injured endothelium and that it surrenders its cholesterol to intimal fibroblasts (16). Chemically modified Lp(a) may be even more potent in this regard (17), an observation of potential relevance to the diabetic patient. However, glycosylation or other postsynthetic modifications unique to diabetes have not been reported.

EPIDEMIOLOGY OF Lp(a)

The important epidemiological association of Lp(a) with atherosclerosis was recognized in the early 1970s when several groups found increased amounts of Lp(a) containing pre-β-lipoprotein bands on electrophoresis in the blood of patients with angina or anatomic evidence of atherosclerotic vascular disease (18,19). More recently, among whites and Japanese Americans, Lp(a) has been shown to be an independent correlate of the presence of coronary artery disease (20,21). In the Honolulu Heart Study, men with Lp(a) levels in the upper quartile compared with men in the lower three quartiles had an odds ratio of 2.54 for history of myocardial infarction. Multivariate analysis revealed that the risk conferred by an elevated serum Lp(a) was independent of more traditional risk factors such as high-density lipoprotein (HDL)- and LDL-cholesterol, total cholesterol concentrations, hypertension, smoking, or age (22). Certain inherited Lp(a) phenotypes seem to be correlated with both elevated Lp(a) concentrations and the presence of coronary heart disease (21). We await the results of similar investigations and prospective studies conducted among patients with diabetes or impaired glucose tolerance.

Lp(a) AND DIABETES

In this issue, Levitsky et al. (p. 283) report on the relationship of Lp(a) with glycosylated hemoglobin among groups of white and black diabetic and nondiabetic children. As previously found, blacks in this study had significantly higher levels of Lp(a) than whites (23). Curiously though, only the white diabetic children demonstrated a relationship between glycosylated hemoglobin values and Lp(a) concentrations ($r = 0.46$). Thus, this study suggests that poor diabetic control raises Lp(a) levels among genetically prone individuals and adds another element to the deranged lipid metabolism of hyperglycemia and diabetes.

Note that the sample size in this study was small. Nevertheless, the finding raises a series of intriguing questions. First, it is evident that a mechanistic interrelationship exists between diabetes (or perhaps hyperglycemia) and Lp(a) metabolism. We can deduce that poor glycemic control may increase the synthesis and/or reduce clearance of Lp(a). But why is the relationship detected only among whites? Are the mechanisms governing Lp(a) metabolism different among racially diverse populations? Could these differences be related to various Lp(a) isoforms or to differences in baseline levels?

A second study by Haffner et al. (p. 302) reports on the effect of improved control on Lp(a) levels in 12 insulin-dependent diabetic subjects. The subjects were instructed in intensified insulin therapy and taught to follow an individualized algorithm for insulin-dose adjustment. After 3 wk, the glycosylated hemoglobin and Lp(a) values fell significantly. However, there was no detectable change in total cholesterol or LDL- or HDL-cholesterol.

This study offers some interventional hope to diabetic patients and additional ammunition to advocates of tight metabolic control. However, some strong words of caution are needed in this regard. Lp(a) has not been shown to be an independent risk factor in diabetes; studies broadly addressing the role of Lp(a) in atherosclerosis among diabetic patients are needed. Furthermore, it has not been established that cardiovascular risk is actually improved by lowering Lp(a). However, if it follows the edicts established by most other cardiovascular risk factors, we can hope that well-controlled diabetic patients will have lower rates of coronary artery disease. In any case, the time to advocate routine measurement of Lp(a) in diabetic and nondiabetic patients has not come. We need to learn much more about its metabolism, the role of its various isoforms in promoting atherosclerosis, and the possible postsynthetic alterations of Lp(a) in diabetes that may make it an even more potent protagonist of intimal disease and pathological thrombosis.

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REFERENCES

1. Loscalzo J: Lipoprotein(a): a unique risk factor for atherothrombotic disease. *Arteriosclerosis* 10:672–79, 1990
2. Zenker G, Költringer P, Boné G, Niederkorn K, Pfeiffer K, Jürgens G: Lipoprotein(a) as a strong indicator for cerebrovascular disease. *Stroke* 17:942–45, 1986
3. Gaubatz JW, Heideman C, Gotto AM Jr, Morisett JD, Dahlen GA: Human lipoprotein(a) structural properties. *J Biol Chem* 258:4582–89, 1983
4. Fless GM, ZumMallen ME, Scanu AM: Physicochemical properties of apoprotein(a) and lipoprotein(a−) derived from the dissociation of human plasma lipoprotein(a). *J Biol Chem* 261:8712–18, 1986
5. Tomlinson JE, McLean JW, Lawn RM: Rhesus monkey apolipoprotein(a): sequence, evolution and site of synthesis. *J Biol Chem* 264:5957–65, 1989
6. Krempler F, Kostner GM, Rascher A, Haslauer F, Bolzano K, Sandhofer F: Studies on the role of specific cell receptors in the removal of lipoprotein(a) in man. *J Clin Invest* 71:1431–41, 1983
7. Snyder ML, Fless GM, Polacek D, Scanu AM: Human

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monocyte derived macrophages degrade Lp(a) differently than LDL (Abstract). *Circulation* 82:358, 1990
8. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C: Lp(a) glycoprotein phenotypes. *J Clin Invest* 80:458–65, 1987
9. Drayna DT, Hegele RA, Haas PE, Emi M, Wu LL, Eaton DL, Lawn RM, Williams RR, White RL, Lalovel JM: Genetic linkage between lipoprotein(a) phenotype and a cDNA polymorphism in the plasminogen gene. *Genomics* 3:230–36, 1988
10. Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu Q, Miller CG, Lawn RM, Scanu AM: Partial amino acid sequence of apoprotein(a) shows that it is homologous to plasminogen. *Proc Natl Acad Sci USA* 84:3224–28, 1987
11. Frank SL, Klisak I, Sparks RS, Mohandus T, Tomlinson JE, McLean JW, Lawn RM, Lusis AJ: The apoprotein(a) gene resides on human chromosome 6q 26–27 in close proximity to the homologous gene for plasminogen. *Hum Genet* 79:352–56, 1988
12. Loscalzo J, Fless GM, Scanu AM: Lipoprotein(a) inhibits fibrin dependent enhancement of tissue plasminogen activator activity (Abstract). *Blood* 72:374, 1988
13. Zioncheck TF, Henzel WJ, Kisiel W, Eaton DL: Identification of plasma proteins that specifically associate with apoprotein(a) (Abstract). *Circulation* 82:456, 1990
14. Loscalzo J, Weinfeld M, Fless G, Scanu AM: Lipoprotein(a), fibrin binding and plasminogen activation. *Arteriosclerosis* 10:240–45, 1990
15. Wolf K, Ráth M, Niendorr A, Beingel U, Dietel M: Morphological colocalization of apoprotein(a) and fibrin(ogen) in human coronary atheromas (Abstract). *Circulation* 80 (Suppl. 2):522, 1989
16. Brown MS, Goldstein JL: Plasma lipoproteins: teaching old dogmas new tricks. *Nature* (Lond) 330:113–14, 1989
17. Haberland ME, Fless G, Scanu AM, Fogelmann AM: Modification of Lp(a) by malondialdehyde leads to avid uptake by human monocyte-macrophages (Abstract). *Circulation* 80 (Suppl. 2):163, 1989
18. Frick MH, Dahlen G, Berg K, Valle M, Hekall P: Serum lipids in angiographically assessed coronary atherosclerosis. *Chest* 73:62–65, 1978
19. Berg K, Dahlen G, Borreson AL: Lp(a) phenotypes, other lipoprotein parameters, and a family history of coronary heart disease in middle aged males. *Clin Genet* 16:347–52, 1979
20. Dahlen GH, Guyton JT, Attar M, Farmer JA, Kautz JA, Gotto AM Jr: Association of levels of lipoprotein(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 74:758–65, 1986
21. Seed M, Hoppichler F, Reaveley D, McCarthy S, Thompson GR, Boerwinkle E, Utermann G: Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med* 322:1494–99, 1990
22. Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL: Lp(a) as a risk factor for myocardial infarction. *JAMA* 256:2540–44, 1986
23. Guyton JR, Dahlen GH, Patsch W: Relationship of plasma lipoprotein(a) levels to race and to apolipoproteins. *Arteriosclerosis* 5:265–72, 1985

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