Whither Lipoprotein(a): Is This Lipid Subclass a Causative or Predictive Factor in Diabetic Macrovascular Disease?

Cross-sectional studies in nondiabetic populations have regularly demonstrated that lipoprotein(a) [Lp(a)] is an independent risk factor for coronary artery disease, stroke, and peripheral vascular disease (1–11). Previous cross-sectional studies in overt NIDDM cast significant doubt on the hypothesis that Lp(a) is causally linked to the macrovascular complications of diabetes (12–16). In this issue, Inoue et al. (17) have explored the relationship between Lp(a) and cardiovascular risk factors in a cross-sectional study conducted using a large clinic population in Japan. The subjects were nondiabetic and had no acute illnesses. No relationship could be found between insulin levels (a surrogate for insulin resistance) and Lp(a), despite the expected relationships of insulin with age, BMI, LDL cholesterol, triglyceride, and glucose. Lp(a) homology with plasminogen, its potential interference with fibrinolysis, and accumulation in arteriosclerotic plaques make this lipid subclass an appealing causative candidate for atherogenesis (18–21). However, levels of Lp(a) are under tight genetic control and vary widely among different ethnic and racial groups (22–28). Prospective studies linking Lp(a) with future arteriosclerotic events have been forthcoming; however, there is significant concern regarding the numbers of individuals studied and the case-control designs used (14,29,30). Therapies aimed at affecting levels of Lp(a) have often been inadvisable (e.g., nicotinic acid in NIDDM), but recent studies have pointed out the beneficial effects of hormone replacement therapy in women and the effects of testosterone and thyroid hormone (31–35). Further, there is evidence that Lp(a) often appears to act as an acute-phase reactant, serving as a surrogate for an underlying process (36).

It is now firmly established that early-onset macrovascular disease occurs 1.5- to 2-fold more often in individuals with NIDDM (37). Although hyperglycemia has now been shown to have an independent additive effect on cardiovascular risk in NIDDM, much of the risk of macrovascular complications has been shown to be present with impaired glucose tolerance (IGT), before the onset of overt clinical NIDDM. Insulin resistance and its associated dyslipidemia, truncal obesity, and hypertension are also common companions of IGT, and all in turn are established risk factors for macrovascular disease. Efforts to link Lp(a) to these risks in NIDDM and IDDM have been largely disappointing (37,38). In some studies in IDDM, Lp(a) levels have been shown to vary with levels of glycemic control (38). Therefore, it is appropriate to study the linkage of Lp(a) with evidence of insulin resistance in a homogeneous population before the onset of NIDDM.

Why then is it so difficult to demonstrate an association between Lp(a) levels and macrovascular risk in patients who have IDDM and NIDDM? One possible explanation lies with the various methods used to detect Lp(a). At this point, there is no gold standard for analysis. Methods include the use of antibodies directed against apolipoprotein(a) [apo(a)], electrophoresis, and ultracentrifugation and the use of anti-apo(a) for capture assays with anti–apo B for detection (39). The latter assays are sensitive to variations in isoforms (23) in the calibrator, and levels vary with LDL cholesterol (40). However, assays designed to measure Lp(a) mass do give consistent results in patient samples (41,42). It is possible that particular isoforms (especially those of smaller size) may be responsible for relationships with arteriosclerotic disease in diabetes and that such isoforms are more prevalent (7,25,26,28,43,44). Levels of Lp(a) mass have been found to be inversely related to molecular size. Another possible confounder of such a relationship in diabetes is the increases in levels reported in diabetic and nondiabetic renal disease (45–47). Since overt and incipient renal disease are common in both types of diabetes, levels of Lp(a) in diabetes may reflect underlying renal disease rather than an arteriosclerotic propensity. Also as mentioned above, variations in Lp(a) levels in patients with IDDM have been shown to vary with glycemic control in some studies. A recent publication also warns that apo(a) antigen may degrade when stored in a freezer (48). Lastly, it is entirely possible that cardiovascular risk is conferred by LDL cholesterol, with Lp(a) playing only a permissive role (20,40,42,43). Unfortunately, we are left with a confusing array of data, most of which conflict with an appealing hypothesis. It is clear that if Lp(a) levels are linked to the macrovascular complications of diabetes, then this relationship is complex and is influenced by laboratory methodology, glycemic control, underlying renal disease, genetic control of isoforms, ethnic and racial mix of the population under study, and perhaps other undescribed factors that affect the concentrations of this lipoprotein. The discouraging truth is that a definitive study to prove or disprove this association with diabetes cannot be accomplished until we fully understand mechanisms of Lp(a) expression and regulation and take these factors into account in a thoroughly defined population.

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