COMMENT ON YE ET AL.

The Association Between Circulating Lipoprotein(a) and Type 2 Diabetes: Is It Causal?

Diabetes 2014;63:332–342

Excess levels of lipoprotein(a) [Lp(a)] has long been recognized as a cause of coronary heart disease (CHD), though the association of Lp(a) with diabetes risk has challenged medical researchers for several reasons, mainly because the association shape is fundamentally a U-shaped one. Ye et al. (1) have newly confirmed such an inverse association in the combined sex of the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, after the first demonstration in the Women’s Health Study (2). Hazard ratios of the bottom to top Lp(a) quintile corresponded to a significant 1.59. The authors analyzed the effect of the single nucleotide polymorphism (SNP) rs10455872 on elevating circulating Lp(a), which failed to be associated with risk of diabetes. They concluded that elevated Lp(a) levels were not causally associated with lower diabetes risk.

This conclusion is misleading because it disregards autoimmune activation as a fundamental pathophysiology of diabetes and other chronic diseases (3–5). Serum Lp(a) is a proinflammatory protein that activates or is itself involved in aggregating to autoimmune components, such as apolipoprotein A-I or adiponectin, resulting in apparently “reduced” Lp(a) levels secondary to a mechanism of immune complex formation and interfered Lp(a) assay results due to failure by capture antibodies (4). Thus, it is the oxidative stress along with autoimmune activation that primarily causes autoimmune-based diabetes.

We have evidence that the amount of “differential” Lp(a) [e.g., lower serum Lp(a) levels than expected], based on an adjustment of SNP rs10455872 genotype, sex, total cholesterol, and fasting insulin, is a significant independent predictor of future diabetes, additively to waist girth and fasting insulin (5). It is the common AA genotype of this SNP that is usually associated with lower serum Lp(a) levels and, in women, with a setting of proinflammatory state without protection against insulin resistance leading to autoimmune activation. The rare GA genotype [associated with three to fourfold serum Lp(a)] protects men against insulin resistance, whereas the converse is valid in women.

The pathophysiological significance of apparently “reduced” Lp(a) levels needs to be widely recognized with the purpose of mobilizing new avenues of prevention and treatment of diabetes and other chronic diseases.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References