Are diabetes mellitus and lipoprotein(a) independently or causally associated with an increased cardiovascular risk?

Serum Lp(a) and diabetes mellitus increase the risk of cardiovascular diseases (CVD). However, the relationship between serum Lp(a) and diabetes is poorly characterized, and it is a subject of debate as to whether they are independently or causally associated (1).

One of the atherogenic mechanisms in hyperglycemia is based on enhanced inflammation. Diabetes is associated with increased vascular production of reactive oxygen species (ROS), which causes premature cell apoptosis via reduction of endothelial nitric oxide (NO), resulting in decreased smooth muscle relaxation and antiatherogenic properties, including decreased platelet aggregation and adhesion inhibition (1).

Another important atherogenic mechanism is the lipid fractions effect. Diabetic dyslipidemia consists of elevated triglyceride-rich lipoproteins (VLDLs) and VLDL remnants and low HDL-C levels. LDL particles are converted to smaller, more atherogenic lipoproteins known as "small-dense LDLs." Diabetic dyslipidemia is due to insulin resistance and hyperglycemia. The diminished insulin action increases ApoB synthesis, and the end products of this process are small-dense LDL particles with reduced LDL receptor-binding affinity, greater penetration in the arterial wall, and increased oxidation susceptibility, leading to atherogenesis. The Strong Heart Study showed that there is a stepwise decrease in LDL size according to diabetic status. This association is more striking in women than in men (1).

Vergles (1) demonstrated the influence of hypertriglyceridemia and obesity in men and women with T2DM. The HDL_2-C levels were significantly lower in the presence of one/both factors, while in their absence, HDL_2-C levels in the diabetics were not significantly different from those in the controls. These functionally-defective small-dense HDLs are characterized with defective ApoA1, prone to degradation and rapid renal elimination. This leads to low HDL-C levels in T2DM (1).

Lp(a) is a serum lipoprotein characterized by the presence of glycoprotein(a) linked to apoprotein B-100. Lp(a) is a poor ligand for the LDL receptors. The amino acid sequence of apoprotein(a) is found to be similar to that of the human plasminogen, which supports the hypothesis that the increased risk of premature atherosclerosis and thrombosis associated with elevated Lp(a) levels rises from the molecular mimicry of plasminogen by apo(a).

Studies regarding the association of Lp(a) levels and diabetes are contradictory. There are few T2DM studies with lower Lp(a) in diabetics compared with non-diabetics. Chico (3) found no difference in the mean Lp(a) concentration between diabetic and non-diabetic subjects. In contrast, Ding et al. (2) reported that Lp(a) concentrations seem inversely associated with the prevalence of T2DM, prediabetes, insulin resistance, and hyperinsulinemia. Arauz (3) found a higher mean Lp(a) concentration in a group of T1DM and T2DM subjects but found no association of glycated hemoglobin and Lp(a) in T2DM subjects. In the Singla et al. (3) study, Lp(a) levels were higher in diabetic patients but showed no association with the degree of glycemic control. The elevated Lp(a) levels did not reflect the glycemic status and were also independent of increased LDL: HDL ratio, suggesting different metabolic pathways between LDL and Lp(a). Smaoui et al. (4) found no correlation of Lp(a) and glycemic control in Tunisian patients with T2DM. Positive correlations were observed between the Lp(a) levels and total and LDL-C in all diabetic patients, particularly in diabetic men. Unlühizarci found not only an association between T2DM and Lp(a) but also identified that the diabetic patients with gangrenous foot lesions were those with the highest level of Lp(a) (5).

Therefore, it can be agreed that there is no consensus in the present data as to whether Lp(a) and T2D are independently or causally associated with CVD risk.

The possible association of Lp(a) levels and metabolic and glycemic control is a major point of interest because the serum concentrations of apoprotein(a) and Lp(a) were found to be, to a large extent, genetically determined (1).

According to Fonseca et al. (6), excellent glycemic control per se does not equally impact nontraditional CVD risk factors, but various diabetes medications have different effects. HDL-C was decreased with basal insulin and pioglitazone, whereas Lp(a) was increased with basal insulin therapy alone. Sánchez-Quesada et al. (7) report that improved glycemic control in patients with T2DM has positive lipid profile effects, such as a significant reduction in nonesterified fatty acids and ApoB concentration, increased LDL size, and decreased electronegative LDL proportion. Similarly, the effect of resistant training on CVD risk factors in patients with T2DM is such that reduces glycemic indexes, decreases insulin resistance, downregulates ApoB levels, and decreases ApoB/ApoA-I ratio, but does not lead to an alteration in ApoA-I, Lp(a), hs-CRP, and fibrinogen (8).

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Therefore, until we have a more definite conclusion, Kishitani et al. (9) besides fasting plasma glucose, HbA1c, and OGTT, recommend a set of additional biomarkers, such as GAD antibody, IA-2 antibody, IRI measurement, HOMA-R, HOMA-beta, small-dense LDL-C, and RLP-C. Besides conventional lipid analyses, Lp(a) measuring has a significant role in this set of biomarkers and is recommended for patients with metabolic syndrome, impaired glucose tolerance, and diabetes.

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References

1. Muačević-Katanec D, Reiner Zj. Diabetic dyslipidemia or 'diabetes lipidus'? Expert Rev Cardiovasc Ther 2011; 9: 341-8. **Crossref**
2. Ding L, Song A, Dai M, Xu M, Sun W, Xu B, et al. Serum lipoprotein (a) concentrations are inversely associated with T2D, prediabetes, and insulin resistance in a middle-aged and elderly Chinese population. J Lipid Res 2015; 56: 920-6. **Crossref**
3. Singla S, Kaur K, Kaur G, Kaur H, Kaur J, Jaswal S. Lipoprotein (a) in type 2 diabetes mellitus: Relation to LDL:HDL ratio and glycemic control. Int J Diabetes Dev Ctries 2009; 29: 80-4. **Crossref**
4. Smaoui M, Hammami S, Chaaba R, Attia N, Hamda KB, Masmoudi AS, et al. Lipids and lipoprotein(a) concentrations in Tunisian type 2 diabetic patients; Relationship to glycemic control and coronary heart disease. J Diabetes Complications 2004; 18: 258-63. **Crossref**
5. Unlühizarci K, Muhtaroğlu S, Kabak S, Bayram F, Keleştimur F. Serum lipoprotein (a) levels in patients with diabetic foot lesions. Diabetes Res Clin Pract 2006; 71: 119-23. **Crossref**
6. Fonseca VA, Theuma P, Mudaliar S, Leissinger CA, Clejan S, Henry RR. Diabetes treatments have differential effects on nontraditional cardiovascular risk factors. J Diabetes Complications 2006; 20: 14-20. **Crossref**
7. Sánchez-Quesada JL, Vinagre I, de Juan-Franco E, Sánchez-Hernández J, Blanco-Vaca F, Ordóñez-Llanos J, et al. Effect of improving glycemic control in patients with type 2 diabetes mellitus on low-density lipoprotein size, electronegative low-density lipoprotein and lipoprotein-associated phospholipase A2 distribution. Am J Cardiol 2012; 110: 67-71. **Crossref**
8. Kadoglou NP, Fotiadis G, Athanasiadou Z, Vitta I, Lampropoulos S, Vrabas IS. The effects of resistance training on ApoB/ApoA-I ratio, Lp(a) and inflammatory markers in patients with type 2 diabetes. Endocrine 2012; 42: 561-9. **Crossref**
9. Kishitani Y. Clinical laboratory examination of diabetic patients in conjunction with metabolic syndrome. Rinsho Byori 2009; 57: 1066-74.

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