EDITORIAL

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Lipoprotein(a): a not-so-well-known risk factor for the development of cardiovascular disease in patients with type 2 diabetes mellitus

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Lipoprotein(a) (Lp(a)), first discovered by Kare Berg in 1963, is an independent risk factor for the development of atherosclerotic cardiovascular disease (CVD) [1]. The structure of Lp(a) is similar to that of low density lipoprotein; both complexes contain a lipid core surrounded by apolipoprotein B (apoB), but in Lp(a), a unique apolipoprotein, apolipoprotein A (apo(a)), is covalently bound to apoB via a disulfide bond [1]. Apo(a) shares high sequence homology with plasminogen but has no fibrinolytic activity. Rather, apo(a) enhances coagulation and compromises clot lysis [2]. The plasma concentrations of Lp(a) are (principally) determined genetically and differ according to ethnicity [3]. Caucasians have lower median plasma levels than do Africans, and Chinese and Asian populations have lower levels than do Caucasians [4,5].

In this issue of the *Korean Journal of Internal Medicine*, Lim et al. [6] report that an elevated Lp(a) level is an independent predictor of the development of CVD in Korean patients with type 2 diabetes mellitus (T2DM). This has high importance, as very limited information is available on the range of Lp(a) levels and the association of Lp(a) with CVD in Koreans. The study is particularly meaningful because the cited authors prospectively followed up a relatively large patient cohort for over 10 years. New CVDs developed in 24.2% of patients during the 11.1 years of follow-up. This confirms that patients with T2DM are at a very high risk of CVD. However, the incidence of CVD in the cited study seems to be much higher than those in other recent studies. This may be because all patients were enrolled in 2003 to 2004, the proportion treated with statins was only 11.6%, and the baseline mean glycated hemoglobin (HbA1c) level was relatively high (8.9%). CVD was much more prevalent among patients with mean HbA1c levels > 9.0% than among those with mean HbA1c levels < 7.0% over the study period. The work confirms that strict glycemic control can reduce the CVD risk in patients with T2DM of relatively long duration.

A high Lp(a) level increases the CVD risk, particularly that in high-risk groups. However, it is very difficult to determine the Lp(a) level indicative of risk. Some studies use 30 or 50 mg/dL as the cutoff value; others define high-risk patients as those in the highest quartile or quintile. Lp(a) plasma concentrations differ according to ethnicity [3]; thus, more research is required

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to determine the level associated with CVD risk in Koreans. In a cross-sectional survey of 14,516 apparently healthy Koreans, the 25th percentile, median, and 75th percentile Lp(a) levels were 9.4, 13.2, and 23.8 mg/dL, respectively [7]. These levels were similar to those in the study by Lim et al. [6], of 8.3, 16.7, and 35.1 mg/dL, respectively, in Korean patients with T2DM. The hazard ratio for CVD development was 2.37 for the 4th versus the 1st Lp(a) quartile, and the median Lp(a) level in the 4th quartile was 55.7 mg/dL (range, 43.1 to 75.3).

Generally, Lp(a) levels are not elevated in patients with T2DM compared with nondiabetic subjects. Furthermore, in an earlier report [8], Lp(a) levels were not associated with the duration of diabetes or the extent of hyperglycemia. In another Chinese study, however, serum Lp(a) concentrations were inversely associated with T2DM, prediabetes, and insulin resistance [9]. The question of whether Lp(a) levels differ between males and females remains controversial. Some prospective studies found no significant sex-related difference in Lp(a) concentrations [10,11]. However, in other studies, including that by Lim et al. [6], Lp(a) levels in females were higher than those in males [6,12,13]. In the study by Lim et al. [6], CVD developed more often in females. Therefore, the elevated CVD risk may be associated with the higher Lp(a) levels in females, although other risk factors, including age, need to be compared between males and females.

Plasma concentrations of Lp(a) are (principally) determined genetically; lifestyle modifications (diet and exercise) do not reduce these levels. Statins do not affect Lp(a) levels, but niacin reduces the levels by 20% to 30% [2]. However, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes Trial showed that addition of niacin to statin therapy did not further reduce the number of CVD events [14]. It is thus uncertain whether Lp(a)-reduction therapy can reduce the CVD risk. The Lp(a) level may be pathogenetically associated with CVD, but at present, that level is of limited clinical application when used to stratify risk. Intra-individual long-term variations in Lp(a) levels are very low in the absence of specific treatments; a single determination is usually sufficient to determine the general risk. Some drugs under clinical development have been shown to decrease Lp(a) levels; these include mipomersen, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cholesteryl ester transfer protein (CETP) inhibitors, and eprotirome. The apoB synthesis inhibitor mipomersen decreased Lp(a) concentrations by approximately 30% [2]. Anacetrapib, a CETP inhibitor [1,2] and the thyroid hormone analog eprotirome [2] each decreased Lp(a) levels by approximately 40%. The CVD outcomes of patients taking such drugs would yield valuable information on whether Lp(a)-reduction treatment reduces the incidence of CVD events. Fibrate derivatives increase plasma Lp(a) concentrations in subjects with hypertriglycemia, and changes in such levels were negatively correlated with changes in triglyceride concentrations [15]. This may explain why fibrate exerts a relatively low CVD preventative effect compared with statins. Apart from CVD, the Lp(a) level was also reported to be associated with diabetic retinopathy and nephropathy in patients with T2DM.

In conclusion, the plasma Lp(a) level may be a useful risk factor for the development of CVD in Korean patients with T2DM. However, no clear cutoff value indicative of CVD risk in Koreans has yet been defined. Indeed, even a range of values is lacking. More research is required. Presently, Lp(a) screening can be used only to stratify those at risk of CVD. However, randomized controlled trials exploring whether selective reduction of Lp(a) levels improves cardiovascular outcomes may alter this view in the future.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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