Association of Serum Leptin Levels With Progression of Diabetic Kidney Disease in Patients With Type 2 Diabetes

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RESEARCH DESIGN AND METHODS—This was an observational cohort study of 668 patients with T2D. Patients were classified into three groups by sex-specific tertile of leptin levels. Outcome measurements were the rate of change in estimated glomerular filtration rate (eGFR) and progression to a more advanced stage of albuminuria.

RESULTS—Patients with low or high leptin levels had a steeper eGFR decline (−2.07 and −2.14 mL/min/1.73 m²/year) than those with midrange leptin levels (−0.82 mL/min/1.73 m²/year, P < 0.01), whereas patients with low leptin levels had an elevated risk of progression of albuminuria as compared with those with high leptin levels (hazard ratio 3.125 [95% CI 1.302–7.499]).

CONCLUSIONS—Both low and high serum leptin levels were risk factors for kidney function decline. Meanwhile, lower serum leptin levels were associated with progression of albuminuria.

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and 0.012) and the multivariate models \((P = 0.005\) and 0.006\) (Fig. 1A).

In the ACR cohort, during the mean follow-up period of 3.2 ± 1.6 years, 28 of 266 patients with normoalbuminuria and 6 of 90 patients with microalbuminuria progressed to a more advanced stage of albuminuria, respectively. Patients with the low leptin levels had a significantly elevated risk of progression of albuminuria as compared with those with high leptin levels in the multivariate model (Fig. 1B).

**CONCLUSIONS**—This study suggests both low and high leptin levels are risk factors for kidney function decline in patients with T2D. Meanwhile, patients with low leptin levels had a significantly elevated risk of progression of albuminuria as compared with those with high leptin levels. To our knowledge, this is the first longitudinal study focusing on the association between leptin and DKD.

In the UKPDS (UK Prospective Diabetes Study), smaller waist circumference was paradoxically reported to be associated with an incidence of kidney insufficiency (13). In light of our findings, lower leptin levels resulting from decreased adipose tissue may partly explain the “reverse epidemiology.” Meanwhile, patients with high leptin levels also had a significant, steep decline rate in eGFR. In these patients, unfavorable leptin actions, such as activation of the sympathetic nervous system, rather than beneficial effects, may affect kidney function decline. Moreover, it is necessary that leptin resistance be considered in patients with high leptin levels. Decreases in the beneficial effects of leptin on the kidney, as a result of leptin resistance, may have affected the steep eGFR decline in patients with high leptin levels.

Lower leptin levels were associated with progression of albuminuria as well as kidney function decline. These findings seem to suggest low leptin levels to be a risk factor for progression of DKD. In contrast, unlike the case of kidney function decline, high leptin levels were not a risk factor for progression of albuminuria. This may be partly explained by the higher proportion of renin-angiotensin system blocker users among patients with high leptin levels as compared with those with low leptin levels (Supplementary Tables 1 and 2). Alternatively, this may indicate the differences in the risk factors for two renal outcomes (13).

Our study has several limitations. First, GFR was estimated using only serum creatinine. Second, we did not evaluate time-dependent changes in leptin, HbA1c, lipid profiles, blood pressure, or BMI during the follow-up period. Third, serum leptin levels may need to be determined using blood samples at a certain time because a circadian rhythm of leptin levels in healthy men has been documented (14). Fourth, this study was based on a relatively small cohort, and the occurrences of events in the second outcome measurement were comparatively low. Finally, the study was carried out in a single urban university hospital.

In conclusion, this study provides evidence of both low and high serum leptin levels as risk factors for kidney function decline, and lower serum leptin levels were associated with progression of albuminuria in patients with T2D. These findings need to be confirmed in studies with a larger sample size and in a multicenter design.

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