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

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OBJECTIVE—To clarify the association of serum leptin levels with progression of diabetic kidney disease in patients with type 2 diabetes (T2D).

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 m^2/year) than those with midrange leptin levels (−0.82 mL/min/1.73 m^2/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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Currently, the role of leptin, a unique hormone with pleiotropic effects (1–7), in the pathogenesis of diabetic kidney disease (DKD) remains unclear. Some studies show patients with DKD have higher serum leptin levels than those without DKD (8,9), whereas leptin administration in patients with generalized lipodystrophy has been reported to dramatically improve albuminuria as well as metabolic parameters (10). We conducted this study to clarify the association of serum leptin levels with progression of DKD in patients with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

This was a single-center observational cohort study of Japanese adult patients with T2D. The subjects were recruited from patients presenting at the Diabetes Center, Tokyo Women's Medical University Hospital, during the period between August 2003 and February 2009. Patients with malignant diseases or glomerulonephritis or those who had undergone lower limb amputation or renal replacement therapy were excluded. Patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 also were excluded. Patients were classified into three groups by sex-specific tertile of serum leptin levels. The study was conducted in adherence with the Declaration of Helsinki and was approved by the ethics committee of Tokyo Women's Medical University Hospital.

Serum leptin levels were determined by radioimmunoassay (Human Leptin RIA, Millipore, Billerica, MA). The stage of albuminuria was defined as normoalbuminuria (urinary albumin-to-creatinine ratio [ACR] <30 mg/g), microalbuminuria (ACR 30–299 mg/g), or macroalbuminuria (ACR ≥300 mg/g) by using first morning urine specimen. GFR was estimated using the following equation (11):

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094} \times 0.739 \text{ (if female)}$$

The first outcome measurement was the annual rate of change in eGFR. For each individual, this rate was determined using a simple regression analysis applied to all eGFR values obtained during the follow-up period. Patients were excluded if their follow-up period was <2 years (12). Patients also were excluded if their rate of change in eGFR was ≥5 mL/min/1.73 m^2/year (considered physiologically implausible). The second outcome measurement was the transition to a more advanced stage of albuminuria, established using at least two consecutive urinary ACR measurements.

For statistical analyses, ANCOVA and Cox regression analyses were conducted (SAS version 9.2; SAS Institute, Cary, NC). In the multivariate Cox regression analyses, a stepwise variable-selecting procedure was performed.

RESULTS

Of 668 patients, 380 qualified (mean age 58 ± 13 years; 61.3% male) and 356 (mean age 58 ± 13 years; 58.7% male) were enrolled as the eGFR and ACR cohorts, respectively (Supplementary Fig. 1). Patients with low leptin levels were more likely to have lower BMI and blood pressure and more favorable lipid profiles than those in the other two groups (Supplementary Tables 1 and 2).

During the mean follow-up period of 4.2 ± 1.2 years, the mean rate of change in eGFR was −1.66 ± 3.69 mL/min/1.73 m^2/year in the eGFR cohort. The rate of decline in eGFR in patients with low and high leptin levels was significantly steeper than that in patients with midrange leptin levels in both the univariate ($P < 0.001$

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

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. 1*B*).

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, HbA_{1c}, 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.

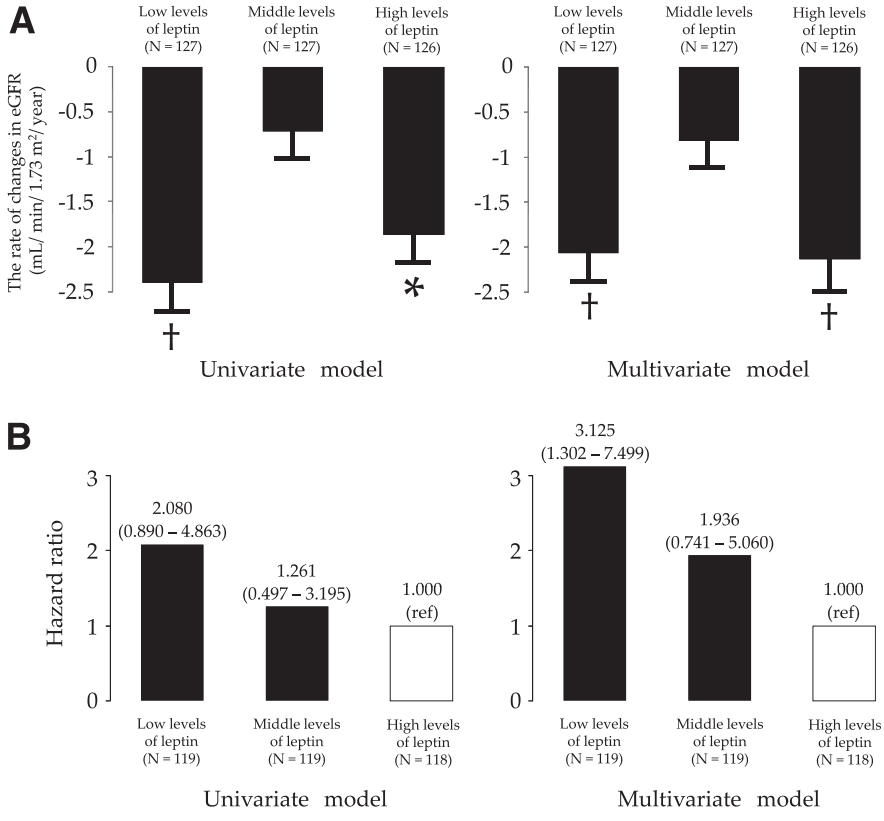

Figure 1—*A: Comparison of the rate of change in eGFR among three groups classified into sex-specific tertile of serum leptin levels. The sex-specific first and second tertile levels of serum leptin were 6.4 and 11.7 ng/mL and 2.9 and 5.2 ng/mL in women and men, respectively. In the multivariate model, the rate of change in eGFR was adjusted by age, sex, systolic blood pressure, BMI, HbA_{1c}, HDL cholesterol, non-HDL cholesterol, eGFR, and logarithmically transformed urinary albumin at baseline (ANCOVA). *P < 0.05 vs. patients with midrange leptin levels. †P < 0.01 vs. patients with midrange leptin levels. B: Hazard ratios for progression of albuminuria among three groups classified into sex-specific tertile by serum leptin levels. The sex-specific first and second tertile levels of serum leptin were 6.3 and 11.7 ng/mL and 2.9 and 5.0 ng/mL in women and men, respectively. In the multivariate model, using a stepwise variable-selecting procedure, the hazard ratio was adjusted by HDL cholesterol and logarithmically transformed urinary albumin at baseline. Age, sex, systolic blood pressure, BMI, HbA_{1c}, non-HDL cholesterol, and eGFR were excluded from the model.*

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