Association of Leptin With Mortality in Patients on Maintenance Hemodialysis
A Prospective Study

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Introduction. Prior studies evaluating the relationship between leptin and outcomes in chronic kidney disease patients have shown conflicting results. Our aim was to evaluate the association of serum leptin with all-cause and cardiovascular disease (CVD)-related mortality in stable maintenance hemodialysis patients.
Materials and Methods. We carried out an observational prospective cohort study of 53 patients on maintenance hemodialysis. The follow-up period was 5 years. Leptin levels were measured at baseline before the start of a hemodialysis session. Proportional hazards models were used to evaluate the relationship between leptin and all-cause and CVD-related mortality.
Results. During the follow-up period, 26 patients (49.1%) died. Fifteen of 26 deaths (57.7%) were attributable to CVD. Cox proportional hazards analysis showed that a leptin level equal to or greate than the median value (3.45 ng/mL) was associated with lower mortality rates (hazard ratio, 0.211; 95% confidence interval, 0.062 to 0.723; P = .01) after multivariable adjustment for potential confounders. However, leptin was not an independent risk factor for CVD-related mortality.
Conclusions. There was a converse association between the serum leptin concentration and mortality in stable maintenance hemodialysis patients. Low serum leptin concentration is an independent risk factor of all-cause mortality in stable maintenance hemodialysis patients, but may not be linked with CVD-related mortality.

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INTRODUCTION

Patients with chronic kidney disease are considered to have a higher risk of death than the general population; cardiovascular disease (CVD) is the major cause of death in these patients. The annual mortality of patients with end-stage renal disease is 15% to 25%.[1] Cardiovascular disease is also the most frequent cause of death in dialysis patients,[2] and the prevalence of vascular calcification is one of important risk factors responsible for CVD in hemodialysis.[3,4] In the dialysis population there are some contradictory observations; conventional risk factors of cardiovascular disease and mortality such as body mass index,[5] serum cholesterol,[6] serum magnesium,[7] and blood pressure[8] are also related to CVD outcomes in maintenance hemodialysis patients, but often in the opposite direction, considered as "reverse epidemiology.[9]" Therefore, more studies are needed to determine the relationship between known risk factors and all-cause and CVD-related mortality in the dialysis population.

Leptin levels are significantly higher in hemodialysis patients than in the general population as a result of a declined renal clearance.[10] The European Uremic Toxin Work Group defined leptin as a member of the middle-molecule toxins in 2003.[11] According to recent studies, leptin levels are related to CVD, possibly due to pro-atherogenic and pro-inflammatory effects in the general population.[12-15] However, the few cross-sectional studies of leptin effects in dialysis patients found varying results.[16-20] Furthermore, prospective data on leptin and prognosis in stable maintenance hemodialysis are lacking. The aim of this study was to evaluate the relationship between serum leptin concentrations and all-cause and CVD-related mortality in a prospective cohort study of patients on maintenance hemodialysis.

MATERIALS AND METHODS

Study Population

A total of 53 patients (23 men and 30 women) with complete baseline data entered our study starting December 2006. Patients were eligible if they had been on hemodialysis therapy for at least 6 months, were 18 years or older, and had no clinically active cardiovascular or infectious diseases. We excluded patients with edema, malignant disease, and liver disorders. They were followed up until death, kidney transplantation, transfer to peritoneal dialysis, or date of censoring, which was January 31, 2012. This prospective observational study was approved by the Ethics Committee of Shengjing Hospital, China Medical University. Informed consent was obtained from all patients before enrollment in the study.

Evaluation of All-cause and Cardiovascular Mortality

Deaths were identified through hospital records and direct contact with patients' families. Deaths owing to CVD included heart failure, myocardial infarction, stroke, and sudden death. We verified CVD as the cause of death from medical record abstraction, death certificates, and information obtained from family members. All materials were independently reviewed by a physician to confirm the cause of death.

Hemodialysis

In our cohort, all of the patients had been undergoing regular 4-hour hemodialysis, 2 or 3 times per week, at a blood flow rate of 200 mL/min to 250 mL/min. Dialysis was performed with biocompatible dialysis membranes that had a 1.5-m^2 surface area. Single-pool urea kinetic model and urea reduction ratio were used to measure the dialysis efficiency, and the median KT/V was 1.27 (range, 1.2 to 1.53). Most patients required antihypertensive medications and recombinant human erythropoietin.

Laboratory Analysis

At the initiation of the study, blood samples were drawn immediately before the start of the hemodialysis session. Plasma was separated within 30 minutes and samples were kept frozen at -70°C. Concentrations of serum albumin, C-reactive protein, parathyroid hormone, calcium, phosphorus, and total cholesterol were measured using routine methods at the Department of Laboratory Medicine, Shengjing Hospital of China Medical University, Shenyang. Serum leptin concentrations were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Statistical Analysis

The participants were categorized into 2 groups using the median serum leptin concentrations as the cutoff point. The Mann-Whitney test and the chi-square test were performed for comparisons between the two groups. Relationships between serum leptin levels and other variables were analyzed using the Spearman correlation coefficient. Survival curves were calculated using the Kaplan-Meier method. Comparison of survival curves was done using the log-rank test. A Cox regressions model were built to assess the association between leptin and mortality and the hazard ratio (HR) and its 95% confidence intervals (CI) were calculated for each variable. For each outcome (all-cause mortality and CVD-related mortality), 3 Cox regression models were fit to the data: nonadjusted, adjusted for age and sex, and adjusted for age, sex, and other potential confounders. *P* values less than .05 were considered significant. All analyses were performed with the SPSS software (Statistical Package for the Social Sciences, version 12.0, SPSS Inc, Chicago, Ill, USA). Data are expressed as the median (interquartile range).

RESULTS

Patients' Characteristics and Leptin

The clinical and biochemical characteristics of the study population are summarized in Table 1. The cause of chronic kidney disease stage 5 was chronic glomerular nephritis in 25 patients (49%), chronic tubulointerstital nephritis in 11 (21%), diabetic nephropathy in 7 (13%), hypertensive nephrosclerosis in 7 (13%), and unknown in 1 (2%). Serum leptin concentration significantly correlated with body mass index (r =0.701; $P < .001$).

Survival and Leptin

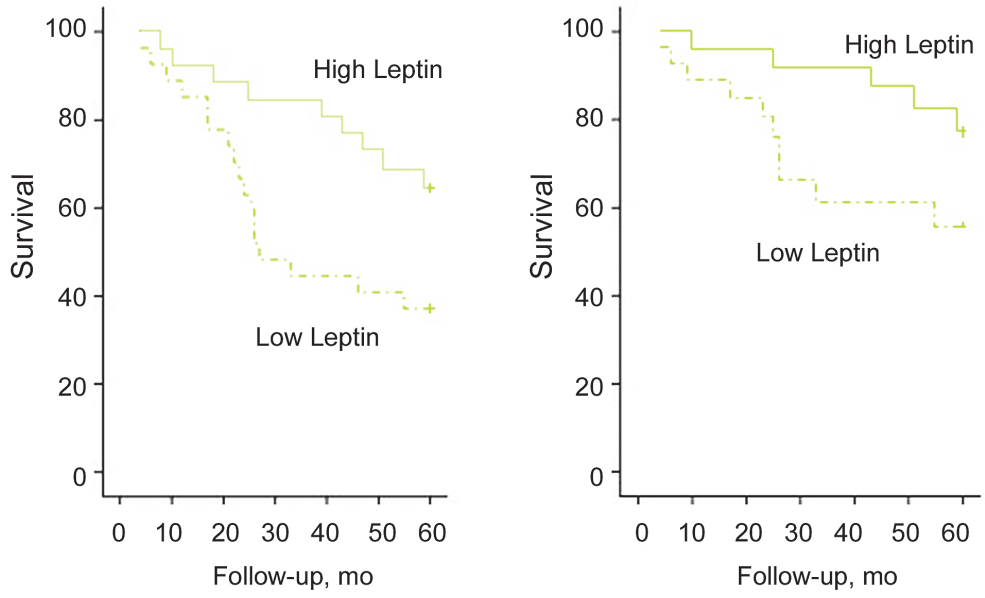
The prospective follow-up period was 5 years. During the follow-up, a total of 26 (49.1%) patients died; 15 (57.7%) of the 26 deaths were attributable to CVD. One patient (1.96%) underwent kidney transplantation and 1 patient (1.96%) was transferred to peritoneal dialysis during the follow-up period. None of the patients were lost to follow up. Deaths occurred a mean of 26.65 ± 15.65 months (range, 4 to 59 months) after the initiation of the study. Serum leptin concentrations at the study entry were lower among the 26 deceased patients (all-cause mortality) compared with those 27 patients who survived ($P = .02$); as shown in Table 1, the median leptin concentration was 2.66 ng/mL (0.87 ng/mL to 6.31 ng/mL) versus 5.75 ng/mL (2.03 ng/mL to 29.85 ng/mL).

The Kaplan-Meier analysis revealed that patients with a serum leptin concentration less than the median (3.45 ng/mL) had a significantly lower survival rate, compared to those whose leptin was equal to or higher than the median (all-cause mortality, chi-squared = 5.070, $P = .02$; CVD-related mortality, chi-squared = 3.274, $P = .07$; Figure).

Cox proportional hazard analysis showed that low leptin concentration (< 3.45 ng/mL) was associated with a higher all-cause mortality; the hazard ratio was 0.211 (95% confidence interval, 0.062 to 0.723; $P = .01$) after multivariable adjustment for potential confounders. Similarly, when leptin concentration was included in the model as a continuous variable, it was associated with all-cause mortality ($P = .02$; Table 2). However, leptin was not an independent risk factor for CVD-related mortality (Table 2).

Table 1. Clinical and Biochemical Characteristics of Hemodialysis Patients by Leptin Concentration

Characteristic	All (n = 53)	Low Leptin Level (n = 27)	High Leptin Level (n = 26)	*P*
Age, y	66 (56 to 70)	64 (56 to 69)	67 (56.00 to 71.25)	.19
Sex				
Male	23 (43.4)	12 (44.4)	11 (42.3)	
Female	30 (56.6)	15 (55.6)	15 (57.7)	.88
Body mass index, kg/m^2	21.78 (18.30 to 23.88)	19.67 (17.33 to 21.99)	23.10 (20.37 to 25.99)	.00
Duration of dialysis, mo	26 (13 to 37)	33 (21 to 37)	25 (13 to 53)	.92
Hemoglobin, g/L	102.00 (86.10 to 115.70)	102.20 (87.20 to 120.00)	101.10 (83.75 to 114.20)	.82
Serum albumin, g/L	38.40 (36.20 to 40.30)	38.90 (34.00 to 40.20)	38.20 (36.40 to 40.52)	.42
C-reactive protein, mg/L	4.39 (2.09 to 10.45)	5.39 (2.17 to 11.30)	3.44 (1.92 to 8.81)	.45
Serum cholesterol, mg/dL	4.41 (3.54 to 5.11)	4.41 (3.56 to 5.15)	4.41 (3.51 to 5.11)	.70
Serum triglyceride, mg/dL	1.35 (1.07 to 1.86)	1.18 (0.94 to 1.43)	1.50 (1.14 to 2.78)	.00
Blood urea nitrogen, mmol/L	26.52 (23.16 to 32.02)	25.73 (21.34 to 28.51)	28.37 (23.90 to 33.08)	.16
Serum creatinine, μmol/L	913.00 (808.35 to 1109.80)	855.70 (732.00 to 1008.00)	957.65 (830.75 to 1193.13)	.03
Serum calcium, mM	2.06 (1.98 to 2.18)	2.05 (1.95 to 2.17)	2.08 (2.03 to 2.20)	.26
Serum phosphate, mg/dL	1.94 (1.27 to 2.35)	1.63 (1.20 to 2.15)	2.02 (1.64 to 2.40)	.08
Parathyroid hormone, pg/mL	163 (66.85 to 370.65)	130.40 (73.30 to 368.70)	165.75 (54.65 to 400.00)	.83
Serum leptin, ng/mL	3.45 (1.12 to 10.91)	1.13 (0.87 to 2.57)	10.91 (5.66 to 34.31)	.00
Leptin/bodymass index, ng·m^2/mL·kg	0.194 (0.06 to 0.46)	0.061 (0.04 to 0.12)	0.43 (0.25 to 1.27)	.00
Serum uric acid, mg/dL	385.50 (349.50 to 471.75)	368.00 (298.00 to 431.00)	416.70 (377.75 to 484.25)	.01
KT/V	1.27 (1.12 to 1.53)	1.25 (1.13 to 1.56)	1.30 (1.08 to 1.52)	.69
Urea reduction ratio	0.67 (0.61 to 0.74)	0.69 (0.63 to 0.75)	0.67 (0.58 to 0.71)	.35
calcium-phosphorus product	47.94 (32.82 to 58.85)	42.35 (29.91 to 52.07)	52.16 (44.88 to 61.34)	.04
Serum bicarbonate, mg/dL	17.90 (14.65 to 20.55)	18.6 (14.90 to 22.30)	17.60 (14.38 to 20.00)	.36
All-cause deaths	26 (49.1)	17 (63.0)	9 (34.6)	.04
Cardiovascular deaths	15 (28.3)	10 (37.0%)	5 (19.2)	.15



Kaplan-Meier survival curves by leptin concentration. Survival curves are displayed for all-cause mortality (**Left**) and cardiovascular mortality (**Right**) in 53 patients on maintenance hemodialysis, categorized by their baseline serum leptin concentration (lower than and equal to or greater than the median leptin concentration).

Table 2. Multivariable Cox Regression Analysis for All-cause and Cardiovascular Disease (CVD)-related Mortality

Parameter	No Adjustment		Adjustment for Age and Sex		Full Adjustment	
	Hazard Ratio (95% Confidence Interval)	*P*	Hazard Ratio (95% Confidence Interval)	*P*	Hazard Ratio (95% Confidence Interval)	*P*
All-cause mortality						
High leptin level	0.406 (0.180-0.915)	.03	0.244 (0.101-0.591)	.002	0.211 (0.062-0.723)	.01
Leptin (per unit change)	0.941 (0.892-0.993)	.03	0.922 (0.858-0.990)	.03	0.909 (0.841-0.983)	.02
CVD-mortality						
High leptin level	0.384 (0.131-1.130)	.08	0.272 (0.084-0.878)	.03	0.207 (0.030-1.433)	.11
Leptin (per unit change)	0.945 (0.0883-1.010)	.10	0.939 (0.87-1.013)	.10	0.929 (0.851-1.014)	.10

*Adjusted for age, sex, body mass index, serum triglyceride, serum creatinine, serum uric acid, and calcium-phosphorus product

DISCUSSION

Our results demonstrated that a low serum leptin concentration was associated with all-cause mortality in stable maintenance hemodialysis patients, but not CVD-related mortality. In this prospective study, we followed up patients for 5 years and our study was carried out in stable maintenance hemodialysis patients. Our results agreed with those of Scholze and coworkers[16]; they found that leptin levels less than the median were associated with a shorter survival in patients with stage 5 chronic kidney disease.[16] Compared with the general population, hemodialysis patients have several distinctive characteristics. The exact role of leptin in patients with established hemodialysis is still vague.

Leptin is synthesized and secreted specifically from white adipose cells. It is well known that leptin interacts with the central nervous system and regulates energy balance. Wallace and associates found, for the first time in a large prospective study, that leptin was an independent risk factor for coronary heart disease.[12] Other clinical studies also found that hyperleptinemia was associated with cardiovascular accidents and acute cerebral vascular events.[13-15,21] Elevated leptin levels may contribute to CVD by promoting endothelial dysfunction, vascular smooth muscle hypertrophy, oxidative stress, vascular inflammation, and vascular calcification; insulin resistance and hypertension both appear to be enhanced by leptin in some diseases.[15,22-24] As a result of a reduced renal clearance, leptin levels are significantly higher in patients with kidney failure than in the general population. Leptin is a member of the middle-molecule toxins and cannot be removed

by regular hemodialysis. It is reasonable that such high leptin levels would contribute to the increased cardiovascular risk and mortality of hemodialysis patients. Interestingly, our results demonstrated that in maintenance hemodialysis patients, a lower serum leptin concentration was associated with all-cause mortality but not with cardiovascular mortality. Consequently, our finding do not support that leptin be considered as a risk factor of all-cause mortality or CVD-related mortality in maintenance hemodialysis patients. Our results, that patients with higher leptin levels survived significantly longer, indicate that leptin does not seem to be a full uremic toxin. Furthermore, it is uncertain that the removal of leptin by high-flux hemodialysis or hemodiafiltration will improve the outcomes of maintenance hemodialysis patients.

There are several explanations for the association of lower leptin levels with an increased susceptibility to mortality in maintenance hemodialysis patients. First, this association is consistent with the theory of "reverse epidemiology" that describes the contradictory relationship between traditional risk factors, such as obesity, hypercholesterolemia, higher plasma homocysteine and hypertension and CVD found in maintenance dialysis patients.[25] Our findings, similar to those reported by Scholze and coworkers and Nasri and colleagues, [16,17] suggest that reverse epidemiology is also true for serum leptin in patients on maintenance hemodialysis therapy. Since characteristics of dialysis patients differ from the general population owing to specific processes of selection and survival, the relationship between the established risk factors and outcomes may have been modified. A similar trend indicated a protective effect of leptin on prognosis in populations with diabetes mellitus,[26] coronary artery disease,[27] and pulmonary arterial hypertension.[28] Another likely explanation is that leptin is not always detrimental to the cardiovascular system. McGaffin and colleagues[29] found that reduced or absent leptin signaling may increase cardiac apoptosis and inflammation, and leptin may play a protective role by decreasing caspase-3 activity and limiting apoptosis in chronic ischaemic cardiac injury. Similar relationships were found in some clinical surveys; a lower leptin level was associated with increased cardiovascular events and poor prognosis in patients with chronic heart disease or type 2 diabetes mellitus.[27,30]

Our results differ from those reported by Diez and colleagues[18] and Beberashvili and colleagues.[19] Both studies found no significant relationship between serum leptin levels and all-cause mortality in hemodialysis patients. First, this difference may have been caused by differences in the genetic background of studied patients. Second, there were different confounding influences of covariates and different laboratory procedures. Finally, our data show that serum leptin concentration was significantly correlated with body mass index and their population had a higher body mass index at baseline than ours. Even these studies also indicate that leptin should not be considered as a full uremic toxin, and that the effect of leptin on mortality in maintenance hemodialysis patients is not always harmful.

Some limitations of the present study should be considered. First, the main limitation is that we only evaluated the relationship between baseline serum leptin levels and mortality during the follow-up. Beberashvili and colleagues[19] found that 1 year of hemodialysis was associated with a significant reduction of plasma leptin levels. As a result, it is better to study the association of longitudinal changes in serum leptin levels with mortality. Second, this study had a relatively small sample size that limited its statistic power. Third, because this study was observational and exposure factors were not manipulated, a definitive cause and effect relationship cannot be presumed for these risk factors. Fourth, classification of CVD was based on clinically manifested events; therefore, the true CVD mortality may have been underestimated. In our study, patients with lower leptin concentrations experienced higher CVD mortality; however, this was only a trend that was not statistically significant, perhaps as a result of the relatively small sample size and underestimated CVD mortality. Nonetheless, the strength of our study is the contribution of long-term longitudinal data that indicate a relationship between low serum leptin and all-cause mortality in stable maintenance hemodialysis patients.

CONCLUSIONS

In summary, the actions of leptin in stable maintenance hemodialysis patient differ from that found in the general population. Our data show that lower serum leptin concentration is an

independent predictor of all-cause mortality in hemodialysis patients. However, further studies are needed to determine whether raising serum leptin concentration will benefit maintenance hemodialysis patients.

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CONFLICT OF INTEREST

None declared.

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