ORIGINAL ARTICLE

Relationship Between Serum Leptin Levels and Body Composition and Markers of Malnutrition in Nondiabetic Patients on Peritoneal Dialysis or Hemodialysis

Abdülkerim Yılmaz*, Mahmut Kayardı, Serhat Icagasioglu, Ferhan Candan, Naim Nur[1], Füsun Gültekin

Departments of Internal Medicine and [1]Public Health, Medical School, Cumhuriyet University, Sivas, Turkey.

Background: Leptin is a protein hormone secreted by adipocytes, regulating body fat and food intake. It has been reported that serum leptin levels are high in patients with chronic renal failure, and this fact has been associated with malnutrition and body composition changes in patients on hemodialysis. This present study investigated the relationship between plasma leptin concentrations and body composition and markers of malnutrition in nondiabetic patients diagnosed with end-stage chronic renal failure, treated with continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD).

Methods: A total of 152 HD and 32 CAPD patients were enrolled into the study. The body compositions of the patients were established by utilizing a Body Composition Analyzer. Triceps skinfold thickness (TSFT) was measured by using a Harpenden Skinfold Caliper. Serum leptin level was detected by radioimmunoassay in ng/mL through employing a DPC Gambyt-CR gamma counter. Standard laboratory methods were used for measuring the remaining parameters (total protein, albumin, blood urea nitrogen, creatinine, hemoglobin, hematocrit, high-sensitivity C-reactive protein [hsCRP]).

Results: No significant difference was observed between the HD and CAPD groups regarding leptin levels. Leptin levels of female patients in both groups were markedly higher when compared with those of men ($p = 0.001$). Plasma leptin levels in total, as well as for both male and female HD and CAPD patients, significantly correlated positively with age, percent fat, fat mass, body mass index and TSFT ($p = 0.001$). Serum leptin levels were not found to be correlated with length of time on dialysis, lean body mass, total body water, hsCRP, total protein and albumin levels ($p > 0.05$).

Conclusion: The data obtained in this study indicated that serum leptin levels could be instrumental markers in establishing body fat ratio, as well as in determining metabolic and nutritional factors in patients with chronic renal failure. [*J Chin Med Assoc* 2005;68(12):566–570]

Key Words: hemodialysis, leptin, malnutrition, peritoneal dialysis

Introduction

Leptin is a protein hormone made up of 167 amino acids synthesized by the *ob* gene located on the 7th chromosome. Its major role in regulating energy expenditure and food intake has been established by various studies carried out since its discovery.[1] It is known that leptin is a signal to the central nervous system regarding body fat tissue stores. Leptin executes this role through receptors in the hypothalamus.[2,3]

*Correspondence to: Dr. Abdülkerim Yılmaz, Cumhuriyet Üniversitesi Tıp Fakültesi, İç Hastalıkları AD, 58140 SİVAS, TÜRKİYE.
E-mail: kerim@cumhuriyet.edu.tr • Received: November 29, 2004 • Accepted: June 9, 2005

Protein energy malnutrition is common in chronic renal failure (CRF) and is associated with increased mortality and morbidity. Recent studies on leptin, also known as the obesity gene protein, have shown that it has an endocrine function for body composition and food intake. Serum leptin levels have been found to be high in patients with CRF, and this outcome was related to malnutrition and changes in body composition in patients on hemodialysis (HD).[4–6]

Various studies comparing serum leptin levels of patients on HD with those of healthy subjects reported higher leptin levels in HD patients.[7–10] It was proposed that this result was due to the fact that the kidney eliminated serum leptin faster than HD. Merabet et al[8] proposed that elevated leptin levels in patients with CRF could not be entirely justified by impaired renal elimination as their study demonstrated low leptin levels in 2 surgically anephric individuals. The same writers suggested that variations in leptin production or secondary effects of uremia may also be causes of non-renal elimination of leptin, affecting leptin concentrations.

A study conducted on rats indicated that plasma leptin was cleared primarily by the kidney.[11] Lack of leptin in normal urine in that study showed that leptin was completely catabolized from the kidneys. Minor and unstable presence of leptin in the patients' urine was regarded as predictive of low molecular weight proteinuria that could be observed during future renal diseases. Considine et al[12] demonstrated that serum leptin concentration was correlated with body mass index (BMI), as well as the percentage of body fat. The correlation between leptin and body fat mass was reported to be higher in patients with CRF when compared to healthy individuals with normal renal function.[7]

This present study investigated the relationship between plasma leptin concentrations and body composition and markers of malnutrition in non-diabetic patients diagnosed with end-stage CRF, treated with dialysis.

Methods

Subjects

A total of 152 HD patients (72 females and 80 males) undergoing 4 hours of therapy 3 times a week using hollow fiber hemophane dialyzers (GFS Plus 11, Gambro, Stockholm, Sweden) and a total of 32 (15 females and 17 men) continuous ambulatory peritoneal dialysis (CAPD) patients were enrolled into the study. Etiologic breakdown of renal insufficiency for the patients in the study was established as follows: chronic glomerulonephritis (n = 41), hypertensive nephrosclerosis (n = 40), obstructive nephropathy (n = 23), chronic pyelonephritis (n = 27), familial Mediterranean fever amyloidosis (n = 9), polycystic kidney (n = 9), lupus nephritis (n = 3) and undefined (n = 32). Patients with diabetes, liver dysfunction, acute infection episodes, surgical operations or a history of corticosteroid use within the last 6 months were excluded.

Blood samples and measurement

Blood samples drawn after an overnight fast were collected in tubes containing disodium EDTA. Plasma was centrifuged at 4°C and kept frozen at –40°C until the measurement of leptin concentration.

Serum leptin level was detected by radioimmunoassay in ng/mL through employing a DPC Gambyt-CR gamma counter (DPC Diagnostic Products Corporation, Los Angeles, CA, USA) at the Department of Nuclear Medicine. A DSL-23100 ACTIVE® Leptin Coated-Tube Immunoradiometric Assay Kit (DSL Diagnostic Systems Laboratories Inc, Webster, TX, USA) was used to measure serum leptin levels. Standard laboratory methods were employed for the measurements of the remaining parameters (total protein, albumin, blood urea nitrogen, creatinine, hemoglobin, hematocrit, high-sensitivity C-reactive protein [hsCRP]).

Body composition

Body fat mass and fat free mass (lean mass) were directly measured by the Body Composition Analyzer (Tanita Corp, Tokyo, Japan). In HD and CAPD patients, measurement was performed after dialysis, and body weight in this study indicates "dry weight". Then BMI, fat mass index (FMI), and lean mass index (LMI) were calculated by dividing body weight (kg), fat mass (kg), and lean mass (kg) by the square of height (m^2), respectively.

Triceps skinfold thickness (TSFT) was measured at halfway between the acromion process and olecranon process in the non-fistula arm on the dorsal surface with a Harpenden Skinfold Caliper of 1/10 sensitivity by taking the mean value of at least 3 measurements of 15-second intervals.

Statistical analysis

Results are given as mean ± standard error (SE). Student's t test and Mann-Whitney U test were used in making group comparisons. Partial correlation coefficient was used to investigate the relationship between groups of data (controlling for age).

Results

Mean (± SE) plasma leptin level was 32.24 ± 2.85 ng/mL for HD patients, and 38.23 ± 6.56 ng/mL for CAPD patients. Leptin levels were significantly higher in females than males in both the HD and CAPD groups ($p = 0.001$). The clinical characteristics of the subjects are shown in Table 1.

Plasma leptin levels positively correlated significantly with age, percent fat, fat mass, BMI and TSFT in males, females and all HD patients ($p = 0.001$). There was, however, no correlation between serum leptin levels and length of time on dialysis, lean body mass, total body water, total protein, albumin and hsCRP levels ($p > 0.05$) (Table 2).

Leptin levels correlated significantly with age, percent fat, fat mass, BMI and TSFT in males, females and all CAPD patients ($p = 0.001$). They did not, however, correlate with length of time on dialysis, lean body mass, total body water, total protein, albumin and hsCRP levels ($p > 0.05$) (Table 2).

Discussion

The kidney is directly involved in leptin clearance. Previous studies reported a leptin gene in the kidneys. It has been demonstrated that in rats, leptin is cleared by the kidneys. Furthermore, arterial-venous differences in leptin concentrations in humans indicate that the

Table 1. Clinical characteristics of hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) subjects*

	Male		Female		Total	
	HD	CAPD	HD	CAPD	HD	CAPD
Patients (*n*)	80	17	72	15	152	32
Age (yr)	48.96 ± 1.78	41.65 ± 2.51	53.13 ± 1.49	45.00 ± 4.62	50.93 ± 1.18	43.22 ± 2.52†
Length of time on dialysis (mo)	61.68 ± 4.89	32.76 ± 3.63†	48.58 ± 4.50	35.80 ± 5.13	55.47 ± 3.37	34.19 ± 3.04†
Height (cm)	167.6 ± 0.76	163.6 ± 2.45	154.6 ± 0.80	155.6 ± 1.21	161.4 ± 0.76	152.6 ± 1.82
Dry body weight (kg)	62.00 ± 1.34	59.94 ± 4.51	63.55 ± 1.83	63.36 ± 4.03	62.73 ± 1.12	61.55 ± 3.02
Body mass index (kg/m^2)	22.28 ± 0.34	22.95 ± 0.80	26.53 ± 0.71	26.26 ± 1.77	24.30 ± 0.42	24.50 ± 0.96
Fat mass index (kg/m^2)	3.86 ± 0.20	4.00 ± 0.58	8.81 ± 0.54	8.49 ± 1.36	6.21 ± 0.34	6.10 ± 0.80
Lean mass index (kg/m^2)	18.58 ± 0.17	19.12 ± 0.52	17.72 ± 0.25	17.78 ± 0.57	18.17 ± 0.16	18.49 ± 0.30
Percent fat mass (%)	16.62 ± 0.66	16.67 ± 1.92	31.30 ± 1.27	29.57 ± 3.51	23.57 ± 0.92	22.72 ± 2.23
Body fat mass (kg)	10.89 ± 0.57	10.99 ± 1.30	21.20 ± 1.32	20.46 ± 3.15	15.77 ± 0.80	15.43 ± 1.81
Lean body mass (kg)	52.28 ± 0.65	54.60 ± 2.25	42.40 ± 0.71	42.97 ± 1.21	34.86 ± 0.46	49.15 ± 1.67
Total body water (kg)	38.28 ± 0.47	40.21 ± 1.45	31.07 ± 0.54	40.21 ± 1.45	34.86 ± 0.46	36.09 ± 1.17
Total protein (mg/dL)	6.66 ± 0.08	6.99 ± 0.17†	6.64 ± 0.08	6.69 ± 0.21	6.55 ± 0.06	6.85 ± 0.14
Albumin (g/dL)	3.57 ± 0.04	3.78 ± 0.11†	3.59 ± 0.05	3.79 ± 0.23	3.57 ± 0.03	3.78 ± 0.22†
Serum leptin (ng/mL)	12.66 ± 2.07	22.91 ± 6.34†	54.02 ± 4.31	55.61 ± 10.53	32.25 ± 2.85	38.23 ± 6.56
High-sensitivity C-reactive protein	8.35 ± 1.05	19.07 ± 7.32	10.80 ± 2.00	11.76 ± 4.25	9.51 ± 1.09	15.64 ± 4.35
Triceps skinfold thickness (mm)	6.98 ± 0.27	7.94 ± 0.66	15.18 ± 0.92	12.13 ± 1.11	10.86 ± 0.56	9.91 ± 0.72

*Values are expressed as mean ± standard error; †$p < 0.05$, Mann-Whitney U test; ‡$p = 0.01$, Student's *t* test.

Table 2. Partial correlation between plasma leptin and other variables (controlling for age)

	Years on dialysis	Percent fat	BMI	TSFT	FM	LM	TBW	Albumin	Total protein	hsCRP
Hemodialysis										
Male	–0.011	0.561*	0.503*	0.288*	0.610*	0.143	0.198	–0.031	0.018	0.039
Female	–0.218	0.740*	0.789*	0.628*	0.772*	0.163	0.240	0.063	0.029	0.100
Total	–0.190	0.813*	0.776	0.716*	0.816*	–0.177	–0.170	0.075	0.024	0.119
Continuous ambulatory peritoneal dialysis										
Male	–0.043	0.774*	0.725*	0.790*	0.737*	–0.074	0.162	–0.132	0.014	0.003
Female	–0.262	0.805*	0.598*	0.481*	0.786*	–0.212	0.258	–0.150	–0.019	0.143
Total	–0.277	0.656*	0.740*	0.168*	0.762*	–0.407	–0.182	–0.156	–0.048	0.130

*$p = 0.01$. BMI = body mass index; FM = fat mass; hsCRP = high-sensitivity C-reactive protein; LM = lean body mass; TBW = total body water; TSFT = triceps skinfold thickness.

kidneys play a major role in leptin elimination. As a result, serum leptin levels are elevated in uremia depending on catabolic defect.[11,13,14]

The rate of leptin clearance from serum determines leptin levels. Impairment of glomerular filtration in patients with renal insufficiency leads to elevated leptin levels, which may cause loss of appetite and protein energy malnutrition in patients with renal insufficiency.[15] Malnutrition is a major comorbid condition in patients with renal insufficiency. Despite numerous interventions to provide nutritional support, malnutrition rates are high in patients with renal insufficiency.[16] Various degrees of malnutrition may be present in 40% of HD patients. This is a critical issue, since most studies investigating nutritional status have reported that malnutrition is correlated with increased morbidity and mortality.[5,17] Leptin levels increase when fat mass increases. Leptin levels were observed to be markedly higher in obese people than in lean people. This result indicates a developed insensitivity to leptin. Studies have demonstrated that leptin levels are significantly correlated with BMI.[12,18]

Nishizawa et al[10] investigated the correlation between leptin levels and body composition in HD patients. They discovered that serum leptin levels were significantly higher in dialysis patients than in healthy individuals. Female subjects in both groups had higher leptin levels. Their study also compared groups with the same percentage of body fat and reported that leptin levels were higher in the group of HD patients with a higher percentage of body fat. Leptin levels correlated positively with BMI and percentage of body fat in dialysis patients, healthy controls and all the subjects together. A similar study conducted on nondiabetic HD patients by Wang et al[19] reported comparable results. Serum leptin levels correlated with body weight, BMI, body fat mass and percentage of body fat for both genders. However, the correlation between serum leptin and percentage of body fat was stronger when compared with that of BMI and fat mass. Young et al[7] observed elevated leptin levels in patients on dialysis and proposed an explanation for this increase as being due to depressed protein intake, lean tissue and malnutrition.

Nakazono et al[9] reported significant positive correlation between leptin levels and percentage of body fat, BMI, total cholesterol, low-density lipoprotein cholesterol and triglyceride levels in HD patients. Their study emphasized the fact that no significant difference existed between diabetic and nondiabetic dialysis patients with respect to leptin levels. Furthermore, leptin levels in diabetic patients were demonstrated to be significantly higher in women than in men. Merabet et al[8] stated that leptin levels were higher in patients on dialysis than in healthy controls. They also reported correlation between leptin levels and BMI, but no correlation was observed between leptin levels and the length of time on dialysis and patients' weight.

We investigated leptin levels in nondiabetic patients on CAPD and HD in our study. We examined the relationship between leptin levels and age, gender, method of dialysis and length of time on dialysis. We, furthermore, studied the correlation between leptin levels and percentage of body fat, fat mass, BMI, lean body mass and total body water, which are elements of body composition. Moreover, the relationships of serum leptin level with TSFT, serum albumin and total protein levels, which are indications of malnutrition in patients with renal insufficiency, were investigated. Positive significant correlations were observed between plasma leptin levels and age, percent fat, fat mass, BMI and TSFT in HD and CAPD patients in this study. These positive correlations could be attributed to our study population: our patients all came from poor socioeconomic backgrounds, and their diets were composed mostly of carbohydrates but not many available proteins. However, serum leptin levels did not correlate with length of time on dialysis, total body water, lean body mass, total protein, albumin and hsCRP levels.

Male and female patients with the same percentage of body fat were compared with respect to their leptin levels. No significant difference in leptin levels was noted with respect to gender in either of the dialysis groups.

Nakazono et al[9] reported that no significant correlation existed between leptin levels and age, dialysis time, length of time on dialysis, serum total protein and albumin levels. Likewise, Nishizawa et al[10] stated that there was no significant correlation between age and length of time on dialysis. Our study had similar results. Previous studies comparing leptin levels in healthy controls and in dialysis patients reported differences between groups and with respect to gender. Our study demonstrated higher leptin levels in female than in male patients in both dialysis groups.

We did not establish a control group in our study. The data were analyzed in terms of the dialysis method employed. There are many studies demonstrating higher leptin levels in dialysis patients when compared with healthy individuals. Therefore, we did not enroll healthy individuals into our study. The main purposes of this study were to investigate leptin levels in patients on different types of dialysis and to examine the relationship of leptin levels to body composition, as

well as to certain malnutrition markers, as the level of leptin in dialysis membranes may differ, so patients being treated with different types of dialysis may have different body composition and malnutrition criteria.

In conclusion, we did not observe any difference in leptin levels between the dialysis groups. The correlations between leptin and body composition, as well as certain malnutrition markers were similar in both groups. The data obtained in this study indicated that serum leptin levels could be instrumental markers in establishing body fat ratio, as well as in determining metabolic and nutritional factors in patients with CRF.

References

1. Tritos NA, Mantzoros CS. Leptin: its role in obesity and beyond. *Diabetologia* 1997;40:1371–9.
2. Zhang F, Basinski MB, Beals JM, Briggs SL, Churgay LM, Clawson DK, DiMarchi RD, et al. Crystal structure of the obese protein leptin-E100. *Nature* 1997;387:206–9.
3. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998;392:398–401.
4. Swierczynski J, Korczynska J, Szolkiewicz M, Karbowska J, Kochan Z, Nieweglowski T, Kusiak E, et al. Low leptin mRNA level in adipose tissue and normoleptinemia in experimental chronic renal failure. *Exp Nephrol* 2001;9:54–9.
5. Jerin L, Ladavac R, Kuzmanovic G, Dodic D, Griparic D. Subjective general assessment of nutritional status in patients with chronic renal failure and regular hemodialysis. *Acta Med Croatica* 2003;57:23–8. [In Croatian]
6. Caglar K, Hakim RM, Ikizler TA. Approaches to the reversal of malnutrition, inflammation, and atherosclerosis in end-stage renal disease. *Nutr Rev* 2002;60:378–87.
7. Young GA, Woodrow G, Kendall S, Oldroyd B, Turney JH, Brownjohn AM, Smith MA. Increased plasma leptin/fat ratio in patients with chronic renal failure: a cause of malnutrition? *Nephrol Dial Transplant* 1997;12:2318–23.
8. Merabet E, Dagogo-Jack S, Coyne DW, Klein S, Santiago JV, Hmiel SP, Landt M. Increased plasma leptin concentration in end-stage renal disease. *J Clin Endocrinol Metab* 1997;82:847–50.
9. Nakazono H, Nagake Y, Ichikawa H, Makino H. Serum leptin concentrations in patients on hemodialysis. *Nephron* 1998;80:35–40.
10. Nishizawa Y, Shoji T, Tanaka S, Yamashita M, Morita A, Emoto M, Tabata T, et al. Plasma leptin level and its relationship with body composition in hemodialysis patients. *Am J Kidney Dis* 1998;31:655–61.
11. Cumin F, Baum HP, Levens N. Leptin is cleared from the circulation primarily by the kidney. *Int J Obes Relat Metab Disord* 1996;20:1120–6.
12. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334:292–5.
13. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, et al. Identification and expression cloning of a leptin receptor, OB-R. *Cell* 1995;83:1263–71.
14. Sharma K, Considine RV, Michael B, Dunn SR, Weisberg LS, Kurnik BR, Kurnik PB, et al. Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. *Kidney Int* 1997;51:1980–5.
15. Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, Wuhl E, et al. Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *J Am Soc Nephrol* 1998;9:1074–9.
16. Norton PA. Effect of serum leptin on nutritional status in renal disease. *J Am Diet Assoc* 2002;102:1119–25.
17. Mehrotra R, Kopple JD. Nutritional management of maintenance dialysis patients: why aren't we doing better? *Annu Rev Nutr* 2001;21:343–79.
18. Wauters M, Mertens I, Considine R, De Leeuw I, Van Gaal L. Are leptin levels dependent on body fat distribution in obese men and women? *Eat Weight Disord* 1998;3:124–30.
19. Wang JY, Lu KC, Lin YF, Hu WM. Correlation of serum leptin concentrations with body composition and gender in Taiwanese hemodialysis patients without diabetes. *Ren Fail* 2003;25:953–66.