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The association of serum leptin with anthropometric indices, lipid metabolism and inflammatory biomarkers in patients with end-stage renal disease undergoing dialysis

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ABSTRACT

Introduction: Introduction: The close link between leptin and kidney function is now concerned that a significant increase in the level of bioactive form of leptin in progressive kidney injuries has been recently revealed.
Objectives: This study assessed the levels of leptin and its main determinants among end-stage renal disease (ESRD) patients on hemodialysis or peritoneal dialysis.
Patients and Methods: This cross-sectional study was performed on 78 patients suffering from ESRD that were planned for hemodialysis (68 patients) or peritoneal dialysis (10 patients) three times a week. The baseline characteristics including demographics, medical history, and medications were collected. The level of laboratory parameters including fasting blood sugar, lipid profile, urea, creatinine, calcium, phosphorus, and parathormone were determined using the special kits.
Results: The mean level of leptin was lower than 7.8 ng/mL in 35.9% of patients Serum leptin of 8.7 to 13.1 ng/mL in 7.7% of cases and higher than 13.1 ng/mL in 56.4% of patients was detected. A direct association of plasma leptin with body weight, body mass index (BMI), and serum levels of triglyceride, total cholesterol, LDL-C, VLDL and uric acid was seen. Serum levels of leptin were adversely associated with the duration of dialysis. In other patients who underwent peritoneal dialysis, the serum levels of leptin were significantly related to leptin with body weight and BMI while adversely with the duration of dialysis. Regarding association of inflammatory markers, this hormone was adversely associated with levels of β2 microglobulin in the hemodialysis group but not in the peritoneal dialysis group. The level of leptin was not associated with the concentrations of IL6 and IFN-γ in both dialysis groups.
Conclusion: In ESRD patients undergoing dialysis, the serum level of leptin is associated with lipid metabolism and BMI. These associations are expected more in the hemodialysis group than in the peritoneal dialysis group.

Implication for health policy/practice/research/medical education:
Leptin is an inflammatory hormone that bioactive level of that increases in ESRD patients.
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Original

Introduction

Leptin is 16 kDa peptide produced and secreted by adipose tissue with a multidimensional physiological role (1). For several years, the potential effect of leptin as an appetite suppressor had been discovered that inducing mutations on its coding gene in animal models led to hyperphagia and energy expenditure resulted in obesity (2,3). Later, the appearance of diabetic status and its-related adverse consequences such as diabetic nephropathy in those with mutated gene was also revealed (4,5). In total, different

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metabolic role of this hormone is now discovered as its potential modulatory effects on different vital systems such as cardiovascular system, immune system, musculoskeletal system, sympathetic nervous system and endocrinological and also glycemic regulatory pathways (6-8). The close link between leptin and kidney function is now more concerned. It has been shown a significant increase in the level of bioactive form of leptin in progressive kidney injuries (9, 10). Patients who suffer end-stage renal disease (ESRD) have 2- to 4-fold higher leptin levels than matched controls with a normal glomerular filtration rate (11). More interestingly, the level of this hormone may not decrease by hemodialysis or with peritoneal dialysis (12, 13). Even it seems that the association between renal failure and increased level of leptin is triggered by increased body mass index (BMI). Hence, each unit increase in BMI can increase the likelihood of increasing level of leptin in ESRD patients that may be explained by accompanying inflammatory and metabolic triggering role induced by obesity (14). In total, the assessment of the physiological and metabolic effects of leptin in renal failure patients especially in those undergoing dialysis is vital.

Objectives

The current study aims to assess the level of leptin and its main determinants among ESRD patients on hemodialysis or peritoneal dialysis.

Patients and Methods

Study population

Our cross-sectional study was conducted on 78 patients who suffered ESRD that were planned for hemodialysis (68 patients) or peritoneal dialysis (10 patients) three times a week at Imam Khomeini hospital in Tehran in 2016. The average time for dialysis was 61 months (median of 48 months, range 3 to 259 months). The baseline parameters including demographic information, data on medical history, and oral medications were collected by reviewing the hospital medical recorded files. The level of laboratory parameters including fasting blood sugar, lipid profile, urea, creatinine, calcium, phosphorus, and parathormone were determined using the special kits. The levels of some inflammatory markers including interleukin-6 (IL6) and interferon gamma (IFN-γ) were also determined by the enzyme-linked immunosorbent assay. The plasma level of leptin was assessed by a Radioimmunoassay technique. Before dialysis, systolic and diastolic blood pressures were determined using an automated oscillometric device. The quality of dialysis before and after dialysis was assessed by the Kt/V formula.

Ethical issues

1) The research followed the Tenets of the Declaration of Helsinki. 2) The study was approved by the Institutional Review Board (IRB) and the Medical Ethics Committee of Tehran University of Medical Sciences. This study was conducted as the nephrology fellowship thesis of Parisa Javadian (#Thesis 996) in Tehran University of Medical Sciences.

Statistical analysis

The findings were described as mean ± standard deviation (SD) by absolute frequencies and percentages for quantitative and categorical variables respectively. Normality of data was tested by the Kolmogorov-Smirnoff test. For comparing categorical variables across the study groups, the chi-square test or Fisher's exact test was used while quantitative variables were compared using *t* test or non-parametric Mann-Whitney U test. The association among the quantitative variables was tested by the Pearson correlation test. The statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was applied to analyze. *P* values of 0.05 or less were considered significant in statistical testing methods.

Results

The average age of participants was in total 56 ± 13 years (median 57 years, range 30 to 80 years) and 41 patients (39 in hemodialysis group and 2 in peritoneal dialysis group) were male. The major causes of ESRD in hemodialysis group included hypertension in 35 patients, glomerulonephritis in 16 patients, diabetes mellitus in 10 patients, polycystic kidney disease in 4 patients, urinary reflux in one patient, neurogenic bladder in a patient and renal stone in another patient. The main cause for peritoneal dialysis was hypertension in 5 patients followed by glomerulonephritis in 2 patients, polycystic kidney disease in 2 patients and diabetes mellitus in 1 patient.

The mean level of leptin was lower than 7.8 ng/mL in 35.9%, 8.7 to 13.1 ng/mL in 7.7% and higher than 13.1 ng/mL in 56.4% of patients. As shown in Table 1, in hemodialysis group, there was a positive association of the plasma level of leptin with some baseline parameters including body weight (r = 0.425, $P<0.001$), BMI (r = 0.553, $P<0.001$), serum level of triglyceride (r = 0.607, $P<0.001$), total cholesterol level (r = 0.569, $P<0.001$), LDL-C level (r = 0.453, $P<0.001$), VLDL level (r = 0.580, $P<0.001$), and the level of uric acid (r = 0.809, $P<0.001$) while the level of leptin was adversely associated with the duration of dialysis (r = -0.365, $P=0.002$). In other patients who underwent peritoneal dialysis, the level of leptin was positively associated with body weight (r = 0.657, $P=0.039$), and BMI (r = 0.555, $P<0.001$), while adversely associated with the duration of dialysis (r = -0.710, $P<0.001$). Regarding association of leptin with inflammatory markers, this hormone was adversely associated with the level of β2 microglobulin in hemodialysis group (r = -0.248, $P=0.041$) but not in peritoneal dialysis group (r = -0.092, $P=0.799$). However, the level of leptin was not

Table 1. The association between serum level of leptin and other parameters

Parameter	Peritoneal dialysis group		Hemodialysis group	
	P	*r* coefficient	*P*	*r* coefficient
Weight (kg)	0.039	0.657	<0.001	0.425
Height (cm)	0.535	-0.223	0.1000	-0.187
BMI (kg/m^2)	0.032	0.675	<0.001	0.553
Dialysis time (min)	0.021	-0.710	0.002	-0.365
Dialysis adequacy (Kt/V)	0.925	-0.034	0.557	0.069
Age (y)	0.756	0.113	0.168	0.169
ESR (mm/h)	0.397	0.301	0.137	0.182
CRP (mg/L)	0.286	0.375	0.615	-0.062
FBS (mg/dL)	0.519	0.232	0.855	0.023
Triglyceride (mg/dL)	0.519	-0.232	<0.001	0.607
Blood urea (mg/dL)	0.925	0.034	0.719	0.044
Cholesterol (mg/dL)	0.955	-0.020	<0.001	0.569
HDL (mg/dL)	0.792	-0.096	<0.001	0.511
LDL (mg/dL)	0.574	-0.203	<0.001	0.453
Hemoglobin (g/L)	0.422	-0.287	0.518	0.080
Calcium (mg/dL)	0.657	0.161	0.438	0.069
Phosphorus (mg/dL)	0.746	0.118	0.128	0.187
Uric acid (mg/ dl)	0.579	-0.200	0.047	0.809
ALP (IU/L)	0.184	0.457	0.326	-0.121
Serum albumin (g/dL)	0.902	-0.045	0.140	-0.032
Creatinine (mg/dL)	0.597	0.191	0.795	-0.018
Parathormone (pg/mL)	0.624	0.187	0.886	-0.018
Total protein (g/dL)	0.955	-0.020	0.484	0.086
VLDL (mg/dL)	0.314	-0.355	<0.001	0.580
β2 microglobulin (mg/L)	0.799	0.92	0.041	-0.248
ADMA (mmol/L)	0.610	0.184	0.866	0.021
Interferon-g (pg/mL)	0.610	0.184	0.271	0.135
Interleukin 6 (pg/mL)	0.873	0.058	0.219	-0.151
DBP (mm Hg)	0.439	-0.277	0.648	0.056
SBP (mm Hg)	0.711	0.293	0.435	0.096

BMI, body mass index; CRP, C-reactive protein; ESR, sedimentation rate; FBS, fasting blood sugar; HDL, High-density lipoprotein; LDL, low-density lipoprotein; ALP, alkaline phosphatase; VLDL, very low-density lipoprotein; ADMA, Asymmetric dimethylarginine; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 2. Comparing mean level of parameters between the two dialysis groups

	Peritoneal dialysis group Mean ± SD	Hemodialysis group Mean ± SD
Weight (Kg)	64.4 ± 11.7	67.4 ± 12.9
Height (cm)	157.0 ± 4.9	164.0 ± 8.8
BMI (kg/m^2)	25.8 ± 4.6	24.9 ± 4.5
Dialysis time (min)	21.1 ± 16.9	67.4 ± 58.8
Dialysis adequacy (Kt/V)	2.5 ± 0.8	1.2 ± 0.3
Age (year)	55.8 ± 16.4	56.6 ± 13.2
ESR (mm/h)	93.9 ± 29.7	71.5 ± 30.4
CRP (mg/L)	16.5 ± 8.4	15.3 ± 17.2
FBS (mg/dL)	117.2 ± 55.2	126.8 ± 101.1
Triglyceride (mg/dL)	253.0 ± 109.0	155.0 ± 80.0
Blood urea (mg/dL)	99.5 ± 45.6	126.5 ± 35.6
Cholesterol (mg/dL)	202.0 ± 47.9	146.0 ± 43.3
HDL (mg/dL)	50.0 ± 13.3	35.5 ± 9.7
LDL (mg/dL)	105.5 ± 31.6	76.0 ± 26.9
Hemoglobin (g/dL)	10.8 ± 1.9	10.6 ± 1.4
Calcium (mg/dL)	9.1 ± 0.8	7.9 ± 1.3
Phosphorus (mg/dL)	4.3 ± 1.7	5.7 ± 1.5
Uric acid (mg/dL)	5.6 ± 0.6	6.6 ± 1.2
ALP (IU/l)	269.5 ± 85.0	426.6 ± 437.6
Serum albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.7
Creatinine (mg/dL)	6.4 ± 2.4	7.8 ± 2.0
Parathormone (pg/mL)	196.0 ± 86.3	531.8 ± 70.5
Total protein (gr/dL)	8.0 ± 0.9	7.4 ± 0.8
VLDL (mg/dL)	48.6 ± 21.4	31.4 ± 15.9
β2microglobulin (mg/L)	9.3 ± 2.4	53.9 ± 22.4
ADMA (mmol/L)	13513.4 ± 9158.4	265.3 ± 20.80
Interferon-g (pg/mL)	84.5 ± 71.8	218.5 ± 76.8
Interleukin 6 (pg/mL)	39.4 ± 43.7	82.1 ± 59.0
DBP (mm Hg)	74.0 ± 10.0	75.2 ± 5.3
SBP (mm Hg)	115.6 ± 13.1	130.0 ± 14.0
Leptin (ng/mL)	70.0 ± 40.5	31.1 ± 36.7

BMI, body mass index; CRP, C-reactive protein; ESR, sedimentation rate; FBS, fasting blood sugar; HDL, High-density lipoprotein; LDL, low-density lipoprotein; ALP, alkaline phosphatase; VLDL, very low-density lipoprotein; ADMA, Asymmetric dimethylarginine; DBP, diastolic blood pressure; SBP, systolic blood pressure.

associated with the concentrations of IL6 and IFN-γ in both dialysis groups.

Comparing the mean baseline parameters between the hemodialysis group and peritoneal dialysis group, we found a significantly higher mean weight, as well as higher levels of blood urea, alkaline phosphatase, parathormone, β2 microglobulin, IFN-γ and IL6 in hemodialysis group as compared to peritoneal dialysis (Table 2). In contrast, in those patients who undergoing peritoneal dialysis, higher levels of ESR, triglyceride, total cholesterol, LDL-C, and VLDL compared with hemodialysis group was detected. Interestingly, the level of leptin was found to be higher in peritoneal dialysis than in the hemodialysis group.

Discussion

Various studies could introduce inflammatory indicators as well as nutritional markers (malnutrition and also obesity) as potential risk factors for cardiovascular-related mortality and morbidity especially in ESRD patients. Dialysis can potentially affect the levels of nutritional elements, hormones, enzymes, and other nutritional components. In this regard, paradoxical results have been obtained on the significant changes in leptin concentrations as a vital hormone regulating metabolic parameters following dialysis in ESRD patients. In other words, besides the role of dietary regimens on this marker, the functional status of this marker can be negatively

influenced by renal impairment as well as by hemodynamic changes following dialysis. As shown in our survey, in hemodialysis group, the level of leptin was related to some laboratory markers such as lipid profile and also to anthropometric parameters including weight and BMI while leptin level was negatively associated with duration of dialysis. In fact, higher level of leptin is predicted more in those with hyperlipidemia and hyperuricemia states as well as in obese patients, while lower leptin level was adversely associated with prolonged hemodialysis. The observed relationships were less highlighted in the patients undergoing peritoneal dialysis and thus the effects of the types of dialysis are significantly different on leptin and its association with laboratory markers. According to the powerful role of both leptin and other markers such as lipids, vital elements, and anthropometric indices on metabolic balance, significant changes in such parameters predictable in ESRD patients may explain higher risk for cardiovascular and metabolic risks in ESRD patients. In a study by Kastarinenl et al (15), higher concentrations of leptin and leptin to BMI ratio were higher meaningfully in ESRD group as compared to control group. In another study by Kaur et al (16), higher levels of leptin beside blood sugar, lipid profile, and creatinine are expected when compared to healthy individuals. As also indicated by Ferencsztaneka et al (17), the increased level of leptin was associated with higher levels of lipids especially in obese patients. Our findings are consistent with previous surveys emphasizing the effect of dialysis (particularly hemodialysis) on leptin in parallel with other metabolic parameters. However, inflammatory markers were less affected by the change in leptin, indicating the link of leptin with metabolic indices, but not probably with inflammatory biomarkers needing further assessment.

The association between leptin level and obesity has been exclusively examined. As shown by Kennedy et al (18) obesity and consequential insulin resistance was related to higher leptin level that may be linked to insulin resistance (19), while insulin can stimulate leptin expression (20). Interestingly, the association between the level of leptin and obesity status may be observed only in men not in female emphasizing the mediatory effects of hormonal pathways on the production and secretion of leptin. It has been reported in some animal models that only males show an association of serum leptin with body weight (21,22). In this regard, a higher level of leptin might be due to lower food intake in the male obese individuals (23) that were not focused on our study.

Additionally, the association between leptin level and lipid profile was widely assessed. In this regard, the change in lipoprotein lipase activity has been shown in those with increased intake of leptin (24). It has been obvious that leptin can increase lipoprotein lipase production (25). Moreover, high fat diet has been previously shown as a reason of rapid leptin resistance (26).

Conclusion

In total, the close link between lipid metabolism and leptin status is clearly expected and thus modification of lipid profile is also predicted by leptin treatment.

Limitations of the study

A limitation of our study was small proportion of patients. We suggest multi-centric studies on this aspect of hemodialysis patients.

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Authors' contribution

All authors contributed to the study. SS conducted the research. PJ and SHT prepared the data and prepared the primary draft. All authors read and approved the final manuscript.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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