Leptin Parameters are Associated with Inflammation and Both Anthropometric and Serum Markers of Protein-Energy Wasting in Hemodialysis Patients

Hemodiyaliz Hastalarında Leptin Parametreleri Enflamasyon ve Protein-Enerji Kaybının Serum ve Antropometrik Göstergeleri ile İlişkilidir

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ABSTRACT

OBJECTIVE: Protein-energy wasting (PEW) and inflammation are common and related to increased cardiovascular mortality in hemodialysis (HD) patients. Herein, we aimed to investigate the relationships between adipocytokines, inflammation and serum and anthropometric markers of PEW syndrome in HD patients.

MATERIAL and METHODS: Seventy-four HD patients (mean age=62±13 years, male/female=44/30) were enrolled. Serum leptin, adiponectin and IL-6 levels were measured by ELISA. Anthropometric measurements such as triceps skin fold thickness (TSFT), mid-arm circumference (MAC) were performed. Bioelectrical impedance analysis was also done. The degree of malnutrition was evaluated with subjective global assessment (SGA).

RESULTS: The leptin/fat ratio was associated with serum IL-6 (r=0.32, p=0.008), serum albumin (r= -0.37, p=0.002) and TSFT (r= -0.41, p=0.001). Serum adiponectin levels were positively correlated with serum albumin (r=0.29,p=0.01) and negatively associated with the leptin/fat ratio (r= -0.30, p=0.01). Serum CRP levels were significantly lower in the high adiponectin group (1.20 ±0.92 vs 2.02 ±2.18 μg/mL, p=0.042). On linear regression analysis for predicting the leptin/fat ratio, gender and serum albumin were retained as significant in the model.

CONCLUSION: Serum leptin parameters are associated with inflammation and both anthropometric and serum markers of protein-energy wasting. Adipocytokines may be the link between PEW and inflammation in uremia.

KEY WORDS: Adiponectin, Adipocytokines, Hemodialysis, Inflammation, Leptin, Protein-energy wasting

ÖZ

AMAÇ: Hemodiyaliz (HD) hastalarında protein-enerji kaybı (PEK) ve enflamasyon yaygındır ve artmış kardiyovasküler mortalite ile yakından ilişkilidir. Bu çalışmada, HD hastalarında adipokinler ile enflamasyon ve serum ile PEK sendromunun antropometrik göstergeleri arasındaki ilişkinin araştırılması amaçlanmıştır.

GEREÇ ve YÖNTEMLER: Çalışmaya 74 HD hastası (ortalama yaş= 62+13, erkek/kadın oranı 44/30) alındı. Serum leptin, adiponektin ve IL-6 seviyeleri ELISA ile ölçüldü. Triseps deri kıvrım kalınlığı (TSFT), orta kol çevresi (MAC) gibi antropometrik ölçümler yapıldı. Ayrıca biyoelektrik impedans analizi yapıldı. Malnütrisyon derecesi subjektif global değerlendirme (SGA) testi ile değerlendirildi.

BULGULAR: Leptin / yağ oranının serum IL-6 (r=0,32, p=0,008) ve serum albumin (r= -0,37, p=0,002) seviyeleri ve TSFT (r= -0,41, p=0,001) ile ilişkili olduğu görüldü. Serum adiponektin düzeyleri serum albumini (r=0,29, p=0,01) ile pozitif korele ve leptin/yağ oranı (r= -0,30, p=0,01) ile negatif korele bulundu. Yüksek adiponektin düzeyi olan grupta serum CRP düzeyleri anlamlı olarak düşük bulundu (1,20 ± 0,92 vs 2,02 ± 2,18 μg/mL, p=0,042). Modelde leptin /yağ oranının prediktif değeri için yapılan lineer regresyon analizinde cinsiyet ve serum albümin değeri anlamlı kalmaya devam etti.

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SONUÇ: Serum leptin parametreleri hem enflamasyon ile hem de PEK'in antropometrik ve serum göstergeleri ile ilişkilidir. Adipositokinler, üremik hastalarda, enflamasyon ve PEK arasındaki bağlantı olabilir.

ANAHTAR SÖZCÜKLER: Adiponektin, Adipositokinler, Hemodiyaliz, Enflamasyon, Leptin, Protein-enerji malnütrisyon

INTRODUCTION

Protein-energy wasting (PEW) and inflammation are common and related to increased morbidity and mortality in hemodialysis (HD) patients (1,2). Fat tissue-derived adipocytokines such as leptin, adiponectin and interleukin-6 (IL-6) may play important roles in PEW and inflammation but only a few studies detail these issues in the HD population.

Leptin modulates energy expenditure and has an anorectic effect (3) in experimental models (4) and the non-uremic population (5,6). Stenvinkel et al. found a significant increase in serum leptin concentrations in peritoneal dialysis (PD) patients who lost lean body mass, and hyperleptinemia was suggested to be an important cause of uremic cachexia (7). Increased serum leptin levels have been shown to be associated with lower dietary intake and higher catabolic rate in uremic children (8). Similarly, Young et al. showed that dialysis patients with a higher leptin/fat ratio had lower protein intake and lean body mass (9). Adiponectin has also been proposed to be related to wasting process in dialysis patients (10). Serum leptin levels are associated with C-reactive protein (CRP) in healthy individuals (11,12). Furthermore, leptin possesses cytokine-like properties and increased leptin levels are related to IL-6 and CRP in obesity, metabolic syndrome and diabetes mellitus (13,14). In contrast, adiponectin is known to have anti-inflammatory and anti-atherogenic properties (15).

With this background in mind, adipocytokines may play a causal role in the relationship between PEW and inflammation in HD patients. To test this hypothesis, we aimed to investigate the relationships between adipocytokines, inflammation and serum and anthropometric markers of PEW syndrome in HD patients.

PATIENTS and METHODS

Study Population

Seventy-four chronic HD patients (mean age=62±13 years, male/female=44/30) were enrolled. Patients with malignancy, anorexia nervosa, acute kidney injury, inflammatory bowel syndromes, acute infectious and inflammatory diseases, and malabsorption syndromes other than uremia were excluded. Etiologies of chronic kidney disease were as follows: diabetes mellitus, 23 (31%); hypertension, 12 (16 %); glomerulonephritis, 7 (9.5%); polycystic kidney disease, 7 (9.5%); chronic pyelonephritis, 3 (4%); others, 8 (11%) and unknown, 14 (19%).

Laboratory Analyses

Fasting blood samples were collected before the midweek HD session. Patients were receiving thrice weekly dialysis for 4 hours period with a standard bicarbonate-containing dialysate bath, using a high-flux HD membrane. Blood flow rates ranged from 250 to 300 mL/min, while dialysate flow rate was kept constant at 500 mL/min.

Serum leptin (Invitrogen, CA, USA), adiponectin (Invitrogen, MD, USA) and IL-6 (Invitrogen, CA, USA) levels were measured by enzyme-linked immunosorbent assay (ELISA). Intra and inter-assay CV of these ELISA kits were as follows: leptin, 3.8% and 4.6%; adiponectin, 2.9% and 2.8%; IL-6, 7.7% and 9.3% respectively. Analytic sensitivity of the kits were as follows: leptin, <2 pg/mL; adiponectin, 100 pg/mL; IL-6, <2 pg/mL respectively.

Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated to determine the insulin resistance by using the formula described previously (16): serum glucose (mg/dL) x serum insulin (μu/mL) / 405.

Anthropometric Measurements

Anthropometric measurements such as triceps skin fold thickness (TSFT) and mid-arm circumference (MAC) were performed. Bioelectrical impedance analysis (BIA) was also performed to measure body mass index (BMI), fat mass and ratio. All the BIA measurements were taken after the hemodialysis session. Degree of malnutrition was evaluated with subjective global assessment (SGA) as described elsewhere (17). Accordingly, the "dialysis malnutrition score" consists of seven features: weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat and signs of muscle wasting. Each component has a score from 1 (normal) to 5 (very severe). Thus the malnutrition score is a number between 7 (normal) and 35 (severely malnourished).

Our examinations of the patients conformed to good medical and laboratory practices and the recommendations of the Declaration of Helsinki on Biomedical Research involving Human Subjects. This study was approved by Ethical Committee of Istanbul Medeniyet University, Goztepe Training and Research Hospital (20/M/20.03.12).

Statistical Analysis

Results were expressed as mean ± standard deviation. Data with non-normal distribution were presented as median (interquartile range). Statistical analyses were performed using the Student t-test and χ^2-tests. Correlation coefficients and significance were calculated by Pearson's test. For all the tests, a two-tailed p value of <0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for Social Sciences for Windows version 16.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline demographic and biochemical parameters of the study population are presented in Table I. Age, time on dialysis, BMI, serum leptin, adiponectin and IL-6 levels were similar between males and females. Serum creatinine, uric acid, and leptin/fat ratio were significantly higher, while body fat ratio, SGA, and TSFT were significantly lower in males compared to females (p<0.05).

The leptin/fat ratio was associated with serum IL-6 (r=0.32, p=0.008) and serum albumin (r= -0.37, p=0.002) (Figure 1).The leptin/fat ratio was significantly negatively associated with TSFT (r= - 0.41, p=0.001).

Serum adiponectin levels were positively correlated with serum albumin (r=0.29, p=0.01) and negatively associated with leptin/fat ratio (r= -0.30, p=0.01) whereas serum adiponectin levels were not associated with anthropometric malnutrition parameters. When patients were divided into two groups according to median adiponectin levels, serum CRP levels were significantly lower in the high adiponectin group (1.20 ±0.92 μg/mL vs. 2.02 ±2.18 μg/mL, p=0.042). As expected, serum IL-6 levels tended to be lower in the high adiponectin group (9.64 ± 7.53 vs. 13 ± 10.71 pg/mL, p=0.08).

The HOMA score was significantly associated with age (r= 0.35, p=0.002), fat mass (r= 0.36, p=0.003), fat ratio (r= 0.38, p=0.002), SGA (r= 0.25, p=0.04), and serum triglyceride (r=0.45, p<0.001). Serum leptin and adiponectin parameters were not associated with insulin resistance indicated by the HOMA score.

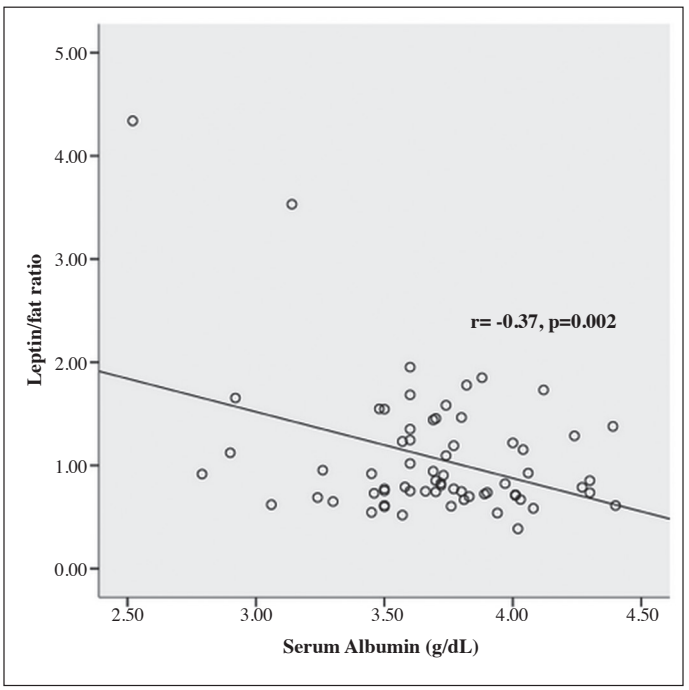

Figure 1: *Leptin/fat ratio was associated with serum albumin levels (r= -0.37, p=0.002).*

When we compared the parameters in patients with and without diabetes, serum leptin levels were significantly lower in diabetic patients compared to non-diabetics (24.19 ± 3.50 ng/mL vs. 25.63 ± 2.34 ng/mL, p=0.03). In contrast, serum adiponectin levels were similar between diabetics and non-diabetics (19.27 ± 11.01 μg/mL vs. 22.58 ± 10.51μg/mL, p=0.20). BMI (25 ± 4 kg/m^2 vs. 22 ± 3 kg/m^2, p=0.001), TSFT (10± 4 mm vs. 6± 4 mm, P=0.001), and MAC values (28± 4 mm vs. 25± 2 mm, p=0.001) were significantly higher in diabetics, while SGA was lower (11 ±4 vs 14 ± 4, p=0.02) in diabetics compared to non-diabetics.

In linear regression analysis for predicting the leptin/fat ratio; age, gender, serum albumin, IL-6 and adiponectin were included as independent variables. Gender and serum albumin were retained as significant in the model (Table II).

DISCUSSION

In the present study, we found serum leptin parameters to be associated with malnutrition and inflammation. Additionally adiponectin had anti-inflammatory features and was negatively associated with serum albumin levels.

Leptin, one of the best characterized adipocytokines, is released into the blood in proportion to the amount of body fat and has inhibitory effects on food intake while increasing energy expenditure (3). Dialysis patients were found to have increased serum leptin levels despite lower body fat ratio when compared to healthy controls (9). The ratio of fat mass is highly variable. Leptin adjusted for an adiposity index such as the fat ratio may be more informative and better correlated with nutritional parameters. Thus we used the leptin/ fat ratio in most of our analyses. Similarly, in the study by Young et al, the leptin / fat mass ratio was used and found as an important indicator of malnutrition (9).

Hyperleptinemia has been shown to be associated with uremic cachexia and lower protein intake in previous studies (7,9). Serum leptin concentrations were found to be increased in PD with low lean body mass (7). It has also been shown that high serum leptin levels are associated with lower dietary intake and higher catabolic rate in uremic children (8). Similarly, patients with higher leptin/fat ratio were found to have lower protein intake and lean body mass (9). In addition to these studies, we found significant associations between serum leptin and anthropometric nutritional parameters such as TSFT. In the study by Young et al, serum leptin concentration was not associated with nutritional indices such as albumin (9). In contrast, we found that the leptin/fat ratio was negatively correlated with serum albumin levels. The discrepancies in the results of the studies might be due to the differences in study populations.

Leptin has also been implicated in many atherogenic processes, including platelet aggregation and thrombosis (18); vascular calcification (19) and production of inflammatory cytokines such as tumor necrosis factor- α (TNF-α), IL-6 and

Table I: Basic biochemical parameters.

Parameters	Total (n=74) Mean ± SD/IQR	Male (n=44) Mean ± SD/IQR	Female (n=30) Mean ± SD/IQR	p value
Age (years)	62 ± 13	61 ± 13	63± 14	0.59
Time on dialysis (years)*	3.13 (1-7.46)	3.13 (1.18-7.38)	3.06 (1-9.56)	0.40
BMI (kg/m^2)	23 ± 3	24 ± 3	22 ± 4	0.18
Fat ratio (%)	27 ± 9	25 ± 9	32 ± 6	**0.001**
Fat mass (kg)	18.84 ± 7.56	18.23 ± 8.03	19.79 ± 6.80	0.41
Lean mass (kg)	48.75 ± 10.49	53.67 ± 9.02	41.09 ± 7.72	**<0.001**
Urea (mg/dL)	137 ± 33	144 ± 32	126 ± 33	**0.02**
Creatinine (mg/dL)	7,65 ± 2,74	8.50 ± 2.80	6.39 ± 2.13	**0.001**
Uric acid (mg/dL)	5,85 ± 1,53	6.17 ± 1.43	5.36 ± 1.58	**0.02**
Calcium (mg/dL)	8,76 ± 0,99	8.71 ± 0.78	8.82 ± 1.25	0.65
Phosphorus (mg/dL)	5,29 ± 1,56	5.47 ± 1.50	5.03 ± 1.65	0.24
Total cholesterol (mg/dL)	172 ± 36	168 ± 35	179 ± 36	0.19
Triglyceride (mg/dL)	162 ± 71	156 ±73	171 ± 69	0.36
HDL (mg/dL)	40 ± 10	38 ± 8	43 ± 12	0.07
LDL (mg/dL)	106 ± 38	106 ± 35	107 ± 43	0.89
ALP (IU/L)*	110 (76-150)	111 (77-141)	104 (65-185)	0.39
Total protein (g/dL)	6,96 ± 0,66	7.02 ± 0.62	6.87 ± 0.71	0.31
Albumin (g/dL)	3,67 ± 0,38	3.70 ± 0.37	3.64 ± 0.39	0.53
Hemoglobin (g/Dl)	10,61 ± 1,49	10.80 ± 1.53	10.32 ± 1.41	0.17
Parathormone (pg/mL)*	307 (183-573)	299 (196-517)	318 (172-695)	0.32
Ferritin (ng/mL)*	545 (293-759)	518 (281-718)	601 (409-868)	0.31
CRP (mg/dL)*	0.98 (0.48-1.91)	0.98 (0.54-2.04)	0.92 (0.39-1.91)	0.49
Insulin (mU/L)*	13.66 (5.70-22.96)	16.13 (5.17-24.66)	12.70 (5.95-21.86)	0.97
HOMA-IR*	3.90 (1.29-7.81)	4.11 (1.19-7.84)	3.21 (1.38-7.62)	0.57
Leptin (ng/mL)	25,12 ± 2,86	25.27 ± 3.08	24.90 ± 2.55	0.59
Leptin / fat ratio	1,07 ± 0,64	1.23 ± 0.76	0.82 ± 0.24	**0.003**
Adiponectin (μg/mL)	21,42 ± 10,73	20.71 ± 10.73	22.47 ± 10.84	0.49
IL-6 (pg/mL)*	9.17 (7.01-11.93)	9.35 (7.46-11.42)	7.92 (6.16-12.68)	0.64
SGA	13 ± 4	11.13 ± 2.52	16.16 ± 5.49	**<0.001**
MAC (mm)	26,12 ± 3,65	26.44 ± 2.86	25.62 ± 4.67	0.44

***** Expressed as median (interquartile range).

BMI: Body mass index, **AST:** Aspartate aminotransferase, **ALT:** Alanine aminotransferase, **ALP:** Alkaline phosphatase, **HDL:** High density lipoprotein, **LDL:** Low density lipoprotein, **ESR:** Erythrocyte sedimentation rate, **TIBC:** Total iron binding capacity, **CRP:** C-reactive protein, **HOMA-IR:** Homeostatic model assessment of insulin resistance, **IL-6:** Interleukin 6, **SGA:** Subjective global assessment, **MAC:** Mid-arm circumference, **TSFT:** Triceps skin fold thickness, **IQR:** Interquartile range

Table II: On linear regression analysis for predicting the leptin/fat ratio, gender, serum albumin and IL-6 were retained as significant in the model.

Model r	0.567			
Adjusted r^2	0.265			
Model p	<0.001			
	Unadjusted		**Adjusted β**	**p value**
	β	**Standard error**		
Constant	4.07	0.85		<0.001
Age (years)	- 0.008	0.005	-0.16	0.12
Gender	-0.37	0.14	-0.28	0.009
Albumin (g/dL)	-0.54	0.19	-0.31	0.006
IL-6	0.01	0.007	0.19	0.08
Adiponectin(μg/mL)	-0.006	0.007	-0.09	0.37

IL-12 (20). Increased leptin levels were found to be associated with increased IL-6 and CRP in obesity, metabolic syndrome and diabetes mellitus (13,14). Leptin directly stimulates the production of acute-phase proteins in liver cells (21). Furthermore, a significant correlation between leptin and CRP concentrations was demonstrated in chronic kidney disesase (CKD) patients, suggesting that inflammation is an important factor that contributes to hyperleptinemia in CKD (22). In the study by Pecoits-Filho et al. (23) performed on 149 non-obese end-stage renal disease (ESRD) patients, a positive correlation was found between IL-6 and serum leptin concentrations. Similarly, we also found a significant association between inflammation and leptin parameters. Adiponectin has been shown to behave as a protective factor for inflammation (24). Consistent with these reports, we also found serum adiponectin levels to be negatively related to serum CRP and IL-6 levels.

Decrease in serum adiponectin levels has been reported to be associated with conditions such as insulin resistance, obesity, diabetes mellitus and dyslipidemia (24-27). However, serum adiponectin levels were not associated with insulin resistance indicated by HOMA score in the present study. Age, serum triglyceride, fat mass and ratio were all significantly correlated with insulin resistance in HD patients, similar to the healthy population. Probably increased adiposity and high serum triglyceride levels are associated with insulin resistance in ESRD patients as well. Adiponectin has been reported to be lower in diabetic patients with early diabetic nephropathy (28) but we could not find any difference in terms of serum adiponectin levels between diabetic and non-diabetic HD patients.

On linear regression analysis for predicting the leptin/fat ratio, gender and serum albumin were retained as significant in the model. Gender was related to the leptin/fat ratio because the fat ratio of the female patients was significantly higher than that of the male patients. Nutritional status indicated by serum albumin was found to be the main factor determining the leptin fat ratio in HD patients.

The cross-sectional nature of the study and lack of follow-up data which might provide important information about the prognostic implications of adipocytokines may be regarded as the limitations of this study.

In conclusion, serum leptin parameters are associated with inflammation and both anthropometric and serum markers of protein-energy wasting in HD patients. Adiponectin seemed to have anti-inflammatory features. Adipocytokines may be the link between PEW and inflammation in uremia.

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