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THE ASSOCIATION BETWEEN LEPTIN AND NUTRITIONAL PARAMETERS IN PERITONEAL DIALYSIS PATIENTS

PERİTON DİALİZ HASTALARINDA LEPTİN VE BESLENME PARAMETRELERİ ARASINDAKİ İLİŞKİ

Rümeyza Kazancıoğlu*, Semra Bozfakıoğlu , Mine Besler" , Nuray Selçuk , Ayşegül Telci , Aydın Türkmen*, Nilgün Aysuna*, Yusuf Orhan", Ergin Ark***

istanbul Faculty of Medicine, Department of Internal Medicine, Division of Nephrology* and Endocrinology****, Department of Microbiology** and Department of Clinical Biochemistry"*, Social Security Istanbul Hospital Dialysis Unit"***, Istanbul, TURKEY

SUMMARY

Protein-calorie malnutrition is an important determinant of morbidity and mortality in dialysis patients. Our objectives were to evaluate nutritional parameters including leptin levels and Kt/V in peritoneal dialysis (PD) patients. Twenty-eight PD patients (13F, 15M) were included in the study. Serum leptin, albumin, prealbumin, transferrin, insulin like growth factor-1 {IGF-I), growth hormone (GH), cholesterol, triglyceride, IgG, IgA, IgM, C3 and C4 levels along with body mass index (BMI) and body fat content (BFC) were determined. The mean leptin level was 26.2 ng/ml. The patients' BMI was 24.4 kg/m^2 and BFC was 27.1%. The serum values were as follows: albumin: 35 g/L, prealbumin: 40.6 mg/dl, transferrin: 2.5 g/L, IGF-]: 169.3 mg/L, GH: 7.9 mg/L, cholesterol: 5.4 mmol/L, triglyceride: 2.4 mmol/L, IgG: 12.9 g/L, IgA: 1.8 g/L, IgM: 1.1 g/L, C3: 1.5 g/L and C4: 0.3 g/L. The Kt/V was measured in 20 of the patients and its mean value was 2.1. No significant correlation was established between leptin levels and Kt/V nor any other parameters other than BMI, albumin, C3 and C4. Our results demonstrated that serum leptin level is elevated and it could only partially serve as a biochemical marker for nutritional status in PD patients.

Key words: Peritoneal dialysis, nutrition, leptin, prealbumin, IGF-1

ÖZET

Diyaliz hastalarında protein-kalori malnütrisyonu morbidite ve mortalitenin önemli bir belirleyicisidir. Çalışmamızda periton diyalizi (PD) hastalarında leptin ile birlikte diğer nütrisyonel parametreler ve Kt/V oranları incelenmiştir. Yirmi sekiz PD (13K, 15E) hastası çalışmaya alınmıştır. Serum leptin, albümin, prealbumin, transferrin, insulin benzeri büyüme faktörü-1 (IGF-]), büyüme hormonu (GH), kolesterol, trigliserid, IgG, IgA, IgM, C3 ve C4 düzeyleri ile birlikte vücut kitle indeksi (BMI) ve vücut yağ oranı (BFC) belirlenmiştir. Ortalama leptin düzeyi, 26.2 ng/ml; BMI, 24.4 kg/m^2 ve BFC, %27.1 olarak bulunmuştur. Diğer sonuçlar ise şu şekildedir: albümin, 35 g/L; prealbumin, 40.6 mg/dl; transferrin, 2.5 g/L; IGF-1, 169.3 mg/L; GH, 7.9 mg/L; kolesterol, 5.4 mmol/L; trigliserid, 2.4 mmol/L; IgG, 12.9 g/L; IgA, 1.8 g/L; IgM, 1.1 g/L; C3, 1.5 g/L ve C4, 0.3 g/L. Yirmi hastada hesaplanabilen Kt/V'nin ortalama değeri 2.1'dir. Leptin düzeyleri ile BMI, albumin, C3 ve C4 değerleri dışında hiç bir parameter ile anlamlı bir korelasyon saptanmamıştır. Sonuç olarak periton diyalizi hastalarında serum leptin düzeyleri yüksek olup; nütrisyonel durum hakkında ancak kismi bir parameter olarak Kabul edilebilir.

Anahtar kelimeler: Periton diyalizi, nütrisyon, leptin, prealbumin

INTRODUCTION

Protein-calorie malnutrition is an important determinant of morbidity and mortality in patients with chronic renal failure, despite many improvements in the treatment of end-stage renal disease (ESRD) (1, 2). Numerous factors contribute to malnutrition such as disturbances of protein and energy metabolism, hormonal imbalances, losses of amino acids into dialysis fluids and especially reduced food intake due to anorexia (2-5).

Leptin with a molecular weight of 16 kDa, a product of *ob* gene, is known to be an inhibitor of appetite and at the same time increases thermogenesis and reduces body fat and weight in rodents (6, 7). It has also been proven that the serum leptin concentration is a good marker of the amount of body fat in obese human subjects (8, 9). Since leptin appears to be catabolized and cleared by the kidney, elevated leptin levels would be expected in chronic renal failure patients and this may have an important influence on the decreased appetite (9-13). Moreover, it may serve as an indicator of nutritional status in addition to simple biochemical measures such as serum albumin, creatinine and blood urea nitrogen (BUN) as well as complex parameters such as prealbumin, transferrin and growth hormone (GH) and insulin-like growth factor I (IGF-1) (1). It is also established that visceral proteins such as albumin, prealbumin and transferrin are affected by any kind of inflammation which makes it difficult to differentiate between undernutrition and inflammation (14, 15).

The aim of our study was to investigate the serum level of leptin as well as other nutritional parameters and their relationship with each other as well as inflammatory markers in peritoneal dialysis (PD) patients.

SUBJECTS AND METHODS

Twenty-eight patients (13 female, 15 male) with a mean age of 43.9+14.6 (range 19-70) years, who were receiving peritoneal dialysis treatment for ESRD were included in this cross-sectional study after giving informed consent. Exclusion criteria were evident causes for anorexia or malnutrition such as HIV infection, malignancy, chronic active hepatitis or bacteriemia.

Renal failure was due to amyloidosis in 1, diabetic nephropathy in 4, reflux nephropathy in 2, adult polycystic kidney disease in 2, chronic pyelonephritis in 4, primary nephrosclerosis in 7 and chronic glomerulonephritis in 8 patients.

The mean duration of PD was 18.7+14.2 (range 2-48) months and only 3 patients were on continuous cycling PD whereas all the others were performing continuous ambulatory PD. All the patients used only various concentrations of dextrose (1.5, 2.5 or 4.25%) dialysate.

Control subjects consisted of healthy and non-obese twenty female and fifteen male volunteers. Their mean age was 33.7+10.1 (range 18-63) years.

All the anthropometric (weight, height and midarm circumference) and plicometric (triceps, biceps, suprailiac and subscapular skinfold thickness) measurements were taken after drainage of PD solution from the abdomen, in an upright position following a normal expirium. Lange skinfold caliper (Cambridge, Maryland) was used for plicometric measurements by the same experienced investigator.

Body mass index (BMI) was calculated by dividing body weight in kilograms into the square of the height in meters. Body fat content (BFC) was calculated from Durnin table (16) using the skinfold thicknesses obtained from four separate sites and was expressed as percentage of body weight.

All nutritional parameters were studied in the fasting plasma samples obtained in the morning after overnight fasting. A human leptin RIA kit (Linco Research Inc, St Charles, MO) was used to determine serum leptin levels. Serum albumin was measured by agarose gel electrophoresis and serum prealbumin and transferrin by single radial immunodiffusion (Behringwerke, AG Marburg, Germany). Serum cholesterol, triglyceride, glucose, BUN and creatinine levels were detected by an auto analyzer using DAX-72 and IGF-1 and GH by immunoradiometric assay (Diagnostic System Laboratory, Webster, TX). Serum immunoglobulins (IgG, IgA and IgM), and complement components C3 and C4 levels were evaluated by nephelometry.

Calculations and Statistical Analysis: Dialysis adequacy was assessed by measuring Kt/V of urea, which was determined by collecting 24-hour drained dialysate and urine specimens followed by blood samples. Kt/V urea was calculated by Baxter PD Adequest 2.0 for Windows.

The results are expressed as mean + SD and range as indicated. Difference of mean values between two groups was evaluated by Student's f-test. Correlation between two variables was examined by Pearson's analysis by using SPSS 8.0 package program (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered significant.

RESULTS

The mean BMI of the patients' was 24.4+4.3 (range 18-31.5) $kg/m^2$and the mean BFC was 27.1+9.4 (range 8.1.-42.9) %. The midarm circumference was 29.0+6.3 (range 22-50) mm.

Peritoneal dialysis patients had a mean serum leptin level of 26.2+30.9 (range 1.6-100) ng/ml. The control group's mean serum leptin level was 9.1+6.0 (range 1.2-24.1) ng/ml ($p<0.01$). The results were also analyzed according to gender. Female controls and

patient groups had higher serum leptin levels than male groups ($p<0.05$). The anthropometric measurements and serum leptin levels of both patient and control groups are presented in **Table I.**

Table II shows the serum concentrations of the other nutritional and inflammatory parameters of PD patients. Of the nutritional parameters, mean BUN, serum creatinine, cholesterol and triglyceride levels were elevated. As of inflammatory parameters, serum IgG, IgA, IgM, C3 and C4 levels were in normal ranges.

Kt/V urea was measured in 20 of the patients with a mean value of 2.1+0.4 (range 1.3-2.7).

Table 1: The anthropometric measurements and serum leptin levels of the control and patient groups.

	Body weight (kg)	BMI (kg/m^2)	Serum leptin (ng/ml)
All control subjects (n=35)	63.8±10.8	23.2±2.9	9.1+6.0
All PD pts (n=28)	64.3+11.1	24.4+4.3	26.2+30.9*
Control female (n=20)	58.8+10.8	22.5+3.3	11.8+6.0
PD female pts (n=13)	60.9+11.4	25.5+4.7	38.9+34.7**
Control male (n=15)	70.5+6.1	24.1±1.9	5.6±3.8
PD male pts (n=15)	67.7+9.6	23.3+3.6	15.1+21.8**

Serum leptin levels correlated with only BMI ($r=0.62$, $p<0.001$) and BFC ($r=0.69$, $p<0.01$) of the nutritional parameters and C3 ($r=0.50$, $p<0.05$) and C4 ($r=0.44$, $p<0.05$) of the inflammatory parameters. The C3 also correlated with BMI ($r=0.62$, $p<0.001$), body weight ($r=0.52$, $p<0.001$) and triglyceride ($r=0.52$,

Table 2: The serum levels of nutritional and inflammatory parameters.

Serum	Mean ± SD	Range	Serum	Mean ± SD	Range
BUN (mmol/L of urea)	20.5±5.5	10.7-36.4	IGF-1 (mg/L)	169.3+99.1	2-336
Creatinine (mmol/L)	777.9+176.8	**495-1105**	GH (mg/L)	7.9+10.8	0.1-49.5
Cholesterol (mmol/L)	5.4+1.6	3.7-7.2	**IgG** (g/L)	12.9+9.7	4.5-16.1
Triglyceride (mmol/L)	2.4+1.8	59-405	**IgA** (g/L)	**1.8+0.9**	0.9-2.4
Albumin (g/L)	35±5	27-42	**IgM** (g/L)	1.1+0.6	0.2-1.9
Prealbumin (mg/dl)	40.6+11.1	16-59	C3 (g/L)	1.5±0.4	0.4-2.3
Transferrin (g/L)	2.5±0.6	1.8-3.8	C4 (g/L)	0.3+0.1	0.1-0.4

$p<0.05$). Immunoglobulins did not correlate with any of the parameters.

DISCUSSION

Malnutrition due to poor food intake is a common clinical problem in patients with ESRD and leads to increased morbidity and mortality (17, 18). An uraemic symptom, anorexia, can be partially corrected with dialysis and despite counseling with dietitians; patients can not always increase their food intake (19). Since the discovery of adipose-derived peptide hormone, leptin, its important role in the reduction of food intake has been reported (11). Previous studies have shown that serum leptin levels are elevated in ESRD since the kidney is responsible for 80% of its clearance (3, 4, 13, 17, 20, 21). Our data also showed that serum leptin levels of PD patients are elevated than healthy controls with matching BMI. At the same time, female patients had significantly higher serum leptin levels than male patients in the PD group, as observed in otherwise healthy population inflicting the role of gender in hyperleptinemia (10, 11).

Leptin concentrations correlated with BMI and BFC, confirming earlier studies using different methods of body fat assessment; thus providing a marker of body composition during PD (19, 22). There was no correlation between serum leptin levels and any of the nutritional parameters. Fontan et al (23) also could not demonstrate any correlation between albumin, prealbumin and midarm circumference with leptin levels. Previous reports have also shown that serum leptin levels were not associated with GH (23). The effect of GH on leptin levels is predicted to be mediated by a reduction in fat mass rather than a direct effect on its secretion (24). We could not find a relation between IGF-1 and leptin, which was proposed to be an important factor in leptin regulation (19, 23). The resistance to the physiological effects of IGF-1 in a uremic environment could have resulted in this lack of association (18). In this study insulin levels were not determined, which could have helped to clarify it's as well as GH and IGF-1 regulatory roles on leptin levels of PD patients.

Another explanation for increased serum leptin in chronic renal failure is an increased synthesis (17, 20, 22). Continuous low-grade inflammation, a frequent event during long term PD, could change the leptin metabolism, since it is shown that leptin synthesis is stimulated by infection, endotoxin and cytokines such as tumor necrosis factor, interleukin 1 and leukemia inhibitory factor (2, 11, 17, 25-27). Stenvinkel et al (28) have shown a significant positive correlation between C-reactive protein (CRP) and serum leptin levels in PD patients, indicating the contributory factor of inflammation to hyperleptinemia. Though CRP was not measured in this study, inflammatory response was determined by immunoglobulins and C3 and C4 levels. Only C3 and C4 correlated with serum leptin levels suggesting that leptin is an important link between nutrition and the immune system.

In conclusion, this study confirms that serum leptin is increased in PD patients and correlated to body mass and fat content. However it can not serve as a marker of nutritional status in this group of patients.

REFERENCES

1. ikizler TA. Biochemical markers: clinical aspects. J Ren Nutr 1997;7:61-64.
2. Stenvinkel P. Leptin-a new hormone of definite interest for nephrologist. Nephrol Dial Transplant 1998;13: 1099-1101.
3. Young GA, Woodrow G, Kendall S, et al. Increased plasma leptin/fat ratio in patients with chronic renal failure: a cause of malnutrition? Nephrol Dial Transplant 1997; 12:2318-2323.
4. Widjaja A, Kielstein JT, Horn R, et al, G. Free serum leptin but not bound leptin concentrations are elevated in patients with end-stage renal disease. Nephrol Dial Transplant 2000;15:846-850.
5. Johansen KL, Mulligan K, Tai V, Schambelan M. Leptin, body composition and indices of malnutrition in patients on dialysis. J Am Soc Nephrol 1998;9:1080-1084.
6. Tsujimoto Y, Shoji T, Tabata T, et al. Leptin in peritoneal dialysate from continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis 1999;34: 832-838.
7. Zhang Y, Proenca R, Mallei M, Barone M, Lori L, Friedman JM. Positional cloning of the mouse *ob* gene and its human homologue. Nature 1994;372:425-432.
8. Considine RV. Weight regulation, leptin and growth hormone. Horm Res 1997;48:116-121.
9. Landt M, Parvin CA, Dagogo-Jack S, Bryant B, Coyne DW. Leptin elimination in hyperleptinaemic peritoneal dialysis patients. Nephrol Dial Transplant 1999; 14: 732-737.
10. Arkouche W, Juillard L, Delawari E et al. Peritoneal clearence of leptin in continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1999;34:839-844.
11. Ahima RS, Flier JS. Leptin. Annu Rev Physiol 2000; 62:413-437.
12. Esler M, Vaz M. Collier G, et al. Leptin in human plasma is derived in part from the brain and cleared by the kidneys. Lancet 1998;351:879-880.
13. Cumin F, Baum HP, Levens N. Leptin is cleared from the circulation primarily by the kidney. Int J Obes 1996;20:1120-1126.
14. ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim RM. Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: a prospective study. Kidney Int 1999;55:1945-1951.
15. Lowrie EG. Acute-phase inflammatory process contributes to malnutrition, anemia, and possibly other abnormalities in dialysis patients. Am J Kidney Dis 1998;6:S105-112.
16. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72. Br J Nutr 1974;32:77-97.

17. Nordfors L, Lonnqvist F, Heimbiirger O, Danielson A, Schalling M, Stenvinkel P. Low leptin gene expression and hyperleptinemia in chronic renal failure. Kidney Int 1998;54:1267-1275.
18. Fouque D. Insulin-like growth factor I resistance in chronic renal failure. Miner Electrolyte Metab 1996; 22:133-137.
19. Fouque D, Juillard L, Lasne Y, et al. Acute leptin regulation in end stage renal failure: the role of growth hormone and IGF-1. Kidney Int 1998;54:932-937.
20. Dagogo-Jack S. Uremic hyperleptinemia: adaptive or maladaptive. Kidney Int 1998;54:997-998.
21. Merabet E, Dagogo-Jack S, Coyne DW, et al. Increased plasma leptin concentration in end stage renal disease. J Clin Endocrinol Metab 1997;82:847-850.
22. Heimbürger O, Lonnqvist F, Danielsson A, Nordenstörm J, Stenvinkel P. Serum immunoreactive leptin concentration and its relation to body fat content in chronic renal failure. J Am Soc Nephrol 1997;8: 1423-1430.
23. Fontan MP, Rodriguez-Carmona A, Cordido F, Garcia-Buela J. Hyperleptinemia in uremic patients undergoing conservative management, peritoneal dialysis and hemodialysis: a comparative analysis. Am J Kidney Dis 1999;34:824-831.
24. Considine RV, Caro JF. Leptin and the regulation of body weight. Int J Biochem Cell Biol 1997;29:1255-1272.
25. Dagogo-Jack S, Ovalle F, Landt M, Gearing B, Coyne DW. Hyperleptinemia in patients with end stage renal disease undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int 1998;18:34-40.
26. Pereira BJ, Poutsiaka DD, King AJ, et al. In vitro production of interleukin-1 receptor antagonist in chronic renal failure, CAPD and HD. Kidney Int 1992; 42:1419-1424.
27. Heimbürger O, Wang T, Lonnqvist F, Stenvinkel P. Peritoneal clearence of leptin in CAPD patients: impact of local insulin administration. Nephrol Dial Transplant 1999;14:723-727.
28. Stenvinkel P, Lindholm B, Lonnqvist F, Katzaarski K, Heimbürger O. Increases in serum leptin levels during peritoneal dialysis are associated with inflammation and a decrease in lean body mass. J Am Soc Nephrol 2000;11:1303-1309.