Hemodialysis International 2014; **18**:153–162

Is there any interaction of resistin and adiponectin levels with protein-energy wasting among patients with chronic kidney disease

Kubra KAYNAR,[1] Birgul V. KURAL,[2] Sukru ULUSOY,[1] Muammer CANSIZ,[1] Buket AKCAN,[2] Nuray MISIR,[3] Selcuk YAMAN,[2] Nuh KAYA[4]

[1]*Department of Nephrology, School of Medicine, Karadeniz Technical University, Trabzon, Turkey;* [2]*Department of Biochemistry, School of Medicine, Karadeniz Technical University, Trabzon, Turkey;* [3]*Department of Forest Management, School of Forestry, Karadeniz Technical University, Trabzon, Turkey;* [4]*Department of Internal Medicine, School of Medicine, Karadeniz Technical University, Trabzon, Turkey*

Abstract

The aim of this study was to evaluate the effects of adipocytokines including adiponectin, leptin, resistin, neuropeptide Y and ghrelin in chronic kidney disease (CKD) patients on appearance of protein-energy wasting (PEW). One hundred fifty patients with mean age of 45.4 ± 15.9 years, without active infections or chronic inflammatory conditions were recruited into the study. Study groups were control group (consisting of 30 healthy volunteers with normal kidney functions), hemodialysis group, predialysis group, peritoneal dialysis group and kidney transplant group. Fasting morning serum leptin, ghrelin, acylated ghrelin, neuropeptide Y, adiponectin, resistin levels of all of the groups were measured. Anthropometric and nutritional assessments of all patients were obtained. Diagnosis of PEW was made according to definition recommended by the International Society of Renal Nutrition and Metabolism. Presence of PEW in hemodialysis (23.3%) and peritoneal dialysis (26.7%) groups were significantly higher than those of predialysis (3.3%), and transplantation (0%) groups. Adiponectin and resistin levels in predialysis, peritoneal dialysis and hemodialysis patients were significantly higher than control group (p: 0.0001). This study had given significant positive correlations between presence of PEW and serum resistin (r: 0.267, p: 0.001), and serum adiponectin levels (r: 0.349, p: 0.0001). There were no relationship between presence of PEW and ghrelin, acylated-ghrelin, neuropeptide Y, and leptin levels of the groups. CKD patients except transplant patients had higher adiponectin and resistin levels than control group. PEW was found to be linearly correlated with resistin and adiponectin. High serum resistin and adiponectin levels might have a role in development of PEW among dialysis patients.

Key words: Leptin, adiponectin, ghrelin, resistin, protein-energy wasting, chronic kidney disease

INTRODUCTION

Protein-energy wasting (PEW) is the state of decreased body stores of protein and energy fuels,[1] and it is relatively common and associated with increased morbidity and mortality in chronic kidney disease (CKD).[2,3] There are several clinical, nutritional, and biochemical parameters

Correspondence to: K. Kaynar, MD, Karadeniz Teknik Üniversitesi, Tıp Fakültesi, Nefroloji Bilim Dalı, Trabzon 61080, Turkey, E-mail: kkaynar@yahoo.com

This study was supported by the Scientific Research Fund of Karadeniz Technical University. No *conflict of interests were* declared.

© 2013 International Society for Hemodialysis

DOI:10.1111/hdi.12072

that may be indicative of PEW in patients with CKD. According to the expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM), PEW is diagnosed if the patient satisfies at least one criteria, in three of the four categories (1. serum chemistry: low serum levels of albumin, transthyretin or cholesterol; 2. body mass: unintentional weight loss over time, decreased body mass index (BMI), or total body fat percentage; 3. muscle mass: decreased muscle mass over time, midarm muscle circumference, or creatinine appearence; and 4. dietary intake: unintentional decreased protein or energy intake.[1]

Mechanisms causing loss of muscle protein and fat are complex, multifactorial and not always associated with low nutrient intake, but are linked to several abnormalities that stimulate protein degradation and or decrease protein synthesis.[4] Several tissues are involved in crosstalk and contribute to metabolic derangements, including adipose tissue, gut, and central nervous system, with mediators including adipocytokines and gastric hormone ghrelin. Adipocytokines were found to be involved in pathogenesis of PEW. Adipocytokines' concentrations in chronic renal failure are mostly elevated probably due to decreased renal excretion. This may lead to clinical implications such as inflamation, loss of appetite, development of PEW syndrome, and progress of atherosclerosis.[5] Some studies have found that end stage kidney disease patients with PEW, low ghrelin and high leptin levels have the highest mortality risk.[6] Uremia leads to an accumulation of the anorexigenic hormones such as desacyl-ghrelin, leptin. Orexigens like acylated ghrelin are not elevated. A disturbed balance between anorexigenic and orexigenic hormones may influence development of CKD-associated PEW. In addition a disturbed balance between proinflammatory adipokines, such as leptin, resistin, and antiinflammatory adipokine, adiponectin may also play a role in CKD-related PEW pathogenesis.

The aim of this study was to evaluate the levels of adipocytokines including adiponectin, leptin, resistin, neuropeptide Y, and gastric hormone ghrelin and acylated ghrelin in CKD patients with different renal replacement treatments and CKD patients with PEW.

PATIENTS AND METHODS

One hundred fifty patients older than 18 years, without active infections or chronic inflammatory conditions (such as patients with active systemic lupus erythematosus disease and elevated C-reactive protein levels) were recruited into the study. Study groups were as follows: group 1, the control group (consisting of 30 healthy volunteers with normal kidney functions with a mean serum creatinine level of 0.75 ± 0.14 mg/dL); group 2, hemodialysis group (30 patients on chronic hemodialysis programme [mean Kt/V of 1.45 ± 0.26] who never underwent a transplant); group 3, predialysis group (30 patients with CKD stage 4 or 5 with a mean creatinine clearance of 19.7 ± 10.2 mL/min); group 4, peritoneal dialysis group (30 patients on chronic peritoneal dialysis programme [mean weekly Kt/V of 2.49 ± 0.78] who never underwent a transplant); and group 5, kidney transplant group (30 patients with functioning kidney allograft average duration of which were 69.3 ± 83.1 months with mean creatinine clearance of 70.4 ± 22.4 mL/min). Inclusion criteria was >18 years. Blood samples (5 mL) of hemodialysis patients were obtained from the arterial line of the hemodialysis before the start of morning session. All of the patients had fasted overnight before the blood samples were taken in the next morning. Blood samples were centrifuged at $3000 \times g$ for 15 min for separation of plasma. Aliquots of plasma samples were stored at –80°C until analyzed.

Serum leptin, ghrelin, acylated ghrelin, neuropeptide Y, adiponectin, resistin levels of all of the groups were measured using enzyme-linked immunosorbent assay (ELISA; sandwich) method with commercial ELISA kit manufactured by DRG (lot number: 45 K032, catalog number: EIA-2395; Marburg, Germany), enzyme immunoassay (EIA) (competitive) method with commercial kit manufactured by Phoenix (lot number: 603182, catalog number: EK-031-30; Burlingame, CA, USA), EIA (sandwich) method with commercial kit manufactured by EIA (lot number: 0438348-1, catalog number: 10006306; Cayman Chemical Company, Ann Arbor, MI, USA), ELISA (competitive) method with comercial kit manufactured by USCN (lot number: L120604048, catalog number: E90879; Hubei, China), Platinum ELISA (sandwich) method with commercial kit manufactured by eBioscinence (lot number:7298504, catalog number: BMS2032; San Diego, CA, USA), and Platinum ELISA (sandwich) method with commercial kit manufactured by eBioscinence (lot number: 74391005, catalog number: BMS2040) respectively. Common biochemical parameters, including urea, creatinine, albumin were measured in all patients and controls, according to standard laboratory methods in the routine clinical laboratory. Previous records of hemodialysis group's single pool Kt/V calculations determined from the predialysis and postdialysis blood urea nitrogen (BUN) levels and the predialysis and postdialysis weights by using the two BUN method described by J. T. Daugirdas[7] were collected. Previous records of protein equivalent of total nitrogen appearance of hemodialysis patients, which were calculated using

the formula protein equivalent of total nitrogen appearance (nPNA) = (0.0136 × [Kt/V × ([predialysis BUN + postdialysis BUN] / 2)]) + 0.251 were collected.[8] Previous records of dialysis adequacy of peritoneal dialysis patients who were assessed via calculations of urea clearance Kt/V from 24-hour urine and dialysate.[9] Previous records of protein equivalent of nitrogen appearance (PNA) of peritoneal dialysis patients which were estimated with 24-hour urine and dialysate collection [the equation is: $6.25 \times (\text{volume}_{\text{urine}} \times \text{concentration of urea}_{\text{urine}}) + (\text{volume}_{\text{dialysate}} \times \text{concentration of urea}_{\text{dialysate}}) + 1.81 + [0.031 \times \text{lean body weight, kg}])]$ were collected.[10] Creatinine clearance and urea clearance of predialysis and kidney transplant patients were recorded.[11] The glomerular filtration rate (GFR) of predialysis and transplant groups were estimated by both modification of diet in renal disease study equation (MDRD) formula (mL/min/1.73 m^2)[12] and by taking average of creatinine and urea clearances (mL/min).[13] Daily protein intake of predialysis patients and transplant patients were estimated from 24-hour urine collections [6.25 (urine urea nitrogen + 30 mg/kg)].[14]

Anthropometric measurements were obtained immediately after the hemodialysis session by a trained researcher. The measurements of skinfold thickness were obtained with the use of skinfold calliper. The measurements were taken at four different sites (biceps, triceps, subscapular and suprailiac). Body fat in percent body weight were estimated from the sum of four skinfold measurements.[15,16] BMI was calculated as body mass (in kg) divided by square stature (in m).[17] Skinfolds and upper midarm circumference (MAC) were measured in the nonfistula side using standard techniques.[15] Midupper arm muscle circumference (MAMC) were calculated with the formula MAC in cm minus triceps skinfold thickness (cm) × Π.[15] The calculations of MAMC were compared with the reference population.[18] The diagnosis of PEW were made according to cut-off points defined on the basis of the consensus of the ISRNM (albumin <4 g/dL for hemodialysis patients, <3.8 g/dL peritoneal dialysis patients and patients with nondialysis dependent CKD; BMI <23 kg/m^2 or total body fat percentage <10%; MAMC, <10th percentile in comparison with the reference population; dietary protein intake <1 g/kg/day for dialysis patients, or <0.5 g/kg/day for patients with nondialysis dependent CKD). Presence of three (must include hypoalbuminemia) out of four criteria is necessary for diagnosis of PEW.[1] The patients were aware of the study and signed an informed consent after reading the document. The study protocol was approved by the Ethics Committee of the School of Medicine at Karadeniz Technical University. All participants gave informed consent.

Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS; version 20.0; SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation (SD) for normally distributed values (at Kolmogorov–Smirnov test) and median (IQ range) for nonnormally distributed values. Differences between groups were established by analysis of variance followed by Dunnet test for normally distributed values and by Kruskall-Wallis variance analysis followed by Mann-Whitney U for nonparametric values. Pearson's and Spearman's correlation coefficient were searched to examine the relation between variables. All results were considered significant if p was <0.05.

RESULTS

A total of 150 patients (89 male, 61 female) with mean age of 45.4 ± 15.9 years, were included into the study. The etiologies of kidney diseases of the patients in groups 2, 3, 4, and 5 were shown in Table 1. The anthropometric and biochemical characteristics of groups (mean ± SD) were illustrated in Table 2. Serum albumin levels of control and kidney transplantation groups were significantly higher than those of predialysis, hemodialysis and peritoneal dialysis groups (p: 0.0001; Table 2). Predialysis patients had significantly the highest BMI, total skinfold measurements, MAMC measurements of all groups (p: 0.009, 0.0001, and 0.0001 respectively; Table 2). nPNA (dietary protein intake) of hemodialysis, predialysis, peritoneal dialysis, and kidney transplant patients were estimated as 0.96 ± 0.21, 0.82 ± 0.21, 0.95 ± 0.3, 1.01 ± 0.24 g/kg/day (Table 2).

None of the kidney transplant patients were observed to have PEW on the other hand 23% of hemodialysis patients and 26.7% of peritoneal dialysis patients were found to have PEW. Both hemodialysis and peritoneal dialysis patients had significantly higher percentage of PEW than those of predialysis group (p: 0.0001; Table 3).

No significant differences in total ghrelin and leptin concentrations were found between the groups (Table 4). On the contrary predialysis, kidney transplant patients and patients on peritoneal dialysis exhibited significantly lower acylated ghrelin levels than those found in the control group (p: 0.003). Neuropeptide Y levels in control, predialysis and hemodialysis groups were similar and significantly higher than those of peritoneal dialysis

Table 1 Etiologies of kidney disease of the patients in groups 2, 3, 4 and 5 [n (%)]

Etiology of kidney disease	Hemodialysis group n (%)	Predialysis group n (%)	Peritoneal dialysis group n (%)	Kidney transplantation group n (%)
Hypertensive nephrosclerosis	11 (36.7)	13 (43.3)	9 (30)	5 (16.7)
Polycystic kidney disease	6 (20)	8 (26.7)	1 (3.3)	3 (10)
Rupture of abdominal aortic aneurysm	2 (6.7)	0 (0)	0 (0)	0 (0)
Vesicoureteral reflux	2 (6.7)	0 (0)	4 (13.3)	2 (6.7)
Amyloidosis	1 (3.3)	0 (0)	0 (0)	0 (0)
Nephrolithiasis	1 (3.3)	1 (3.3)	0 (0)	1 (3.3)
Diabetic nephropathy	4 (13.3)	4 (13.3)	5 (16.6)	1 (3.3)
Glomerulopathies	2 (6.7)	2 (6.7)	5 (16.6)	10 (33.3)
Unknown	0 (0)	1 (3.3)	3 (10)	4 (13.3)
Renal cell carcinoma	1 (3.3)	0 (0)	0 (0)	0 (0)
Cardiorenal syndrome	0 (0)	1 (3.3)	0 (0)	0 (0)
Chronic tubulointerstitial nephritis	0 (0)	0 (0)	1 (3.3)	1 (3.3)
Lupus nephritis	0 (0)	0 (0)	1 (3.3)	0 (0)
Alport syndrome	0 (0)	0 (0)	1 (3.3)	1 (3.3)
Gout	0 (0)	0 (0)	0 (0)	1 (3.3)
Chronic pyelonephritis	0 (0)	0 (0)	0 (0)	1 (3.3)
Total	30 (100)	30 (100)	30 (100)	30 (100)

and transplantation groups (p: 0.0001). Serum adiponectin levels of peritoneal dialysis groups were significantly higher than those of other groups (Figure 1). Hemodialysis group had the second highest serum adiponectin levels (p: 0.0001). Predialysis group were found to have significantly higher adiponectin levels than those of control group, which were similar to those of group 5 (Table 4). Similarly, serum resistin levels of hemodialysis and peritoneal dialysis groups were highest of all of the groups. (p: 0.0001; Figure 2). Resistin levels of predialysis patients were significantly higher than those of control and transplant groups which were found to be similar (Table 4). Coefficients of variation for the measurement of adipocytokines of the groups were illustrated in Table 5. The variation of intragroup adipocytokine measurements might be attributed to differences in BMI, serum albumin, presence of PEW, body fat ratio, creatinine clearance and MAMC values (which were found to be significantly correlated with adipocytokine levels) of patients in the same group.

This study had given significant correlations between serum ghrelin concentrations and BMI (r: –0.195, p: 0.017), MAC (r: –0.179, p: 0.029), and serum acylated ghrelin levels (r: 0.318, p:0.005; Table 6).

Serum acylated ghrelin levels were found to be negatively correlated with weight (r:–0.251, p: 0.03), MAMC (r:–0.340, p: 0.003), creatinine clearance (r:–0.365, p: 0.047), posttransplantation follow-up duration (r:–0.575, p: 0.025), and positively correlated with neuropeptide Y (r: 0.304, p: 0.008), adiponectin (r: 0.271, p: 0.019), and ghrelin levels (r: 0.318, p: 0.005).

Serum leptin levels were found to be significantly negatively correlated with protein nitrogen appearence, GFR with MDRD formula, posttransplantation follow-up duration, While serum leptin levels were found to be positively correlated with total skinfold thickness (Table 6).

Serum resistin and adiponectin levels of peritoneal dialysis and hemodialysis groups were significantly higher than those of control, predialysis and transplantation groups (p: 0.0001). Resistin levels were found to be significantly positively correlated with adiponectin levels and presence of PEW, while significant negative correlations were found between resistin levels and creatinine clearance, serum albumin levels (Table 6). Adiponectin levels were found to be significantly positively correlated with presence of PEW, resistin levels and acylated ghrelin levels, while there were significant negative correlations between adiponectin levels and BMI, total skinfold thickness, serum albumin levels, creatinine clearance, posttransplantation follow-up duration (Table 6).

This study had given significant positive correlations between presence of PEW and serum resistin (r: 0.267, p: 0.001), and serum adiponectin levels (r: 0.349, p: 0.0001). There were no relationship between presence of PEW and ghrelin, acylated-ghrelin, neuropeptide Y and leptin levels of the groups. But presence of PEW was significantly negatively correlated with serum leptin levels and positively correlated with serum adiponectin levels

Table 2 Demographic features, anthropometric characteristics and biochemical measurements of the groups (mean ± SD)

Variables	Control Group	Hemodialysis Group	Predialysis Group	Peritoneal Dialysis Group	Kidney Transplantation Group	P value
Age (years)	33.4 ± 9.4[a,b,c]	49.8 ± 16.1[x]	58.4 ± 15.2[y,z]	39.1 ± 13.4	47.1 ± 13.1	0.0001
Height (cm)	166.5 ± 8.8[d]	166.8 ± 8.4	148.9 ± 50.8	141.7 ± 57.5	167.5 ± 10.4	0.009
Body weight (kg)	67.3 ± 12.6	66.1 ± 13.5[t]	76.4 ± 14.0[y]	66.7 ± 16.2	71.8 ± 12.8	0.019
BMI (kg/m^2)	24.3 ± 3.3[b]	23.9 ± 4.5[t]	27.4 ± 4.5[y]	24.3 ± 4.9	25.5 ± 3.4	0.009
Triceps skinfold thickness (mm)	13.3 ± 4.0	10.9 ± 5.8	14.5 ± 7.5	10.9 ± 5.8	13.3 ± 6.2	NS
Biceps skinfold thickness (mm)	9.5 ± 2.7[a,d]	7.6 ± 4.5	9.9 ± 4.5	7.4 ± 3.2	10.0 ± 4.9	0.013
Suprailiac skinfold thickness (mm)	10.0 ± 4.7[b,c]	12.2 ± 8.6	14.7 ± 7.4	10.1 ± 6.1	14.7 ± 7.7	0.010
Subscapular skinfold thickness (mm)	19.2 ± 5.5[a]	12.9 ± 7.3[t,u]	25.5 ± 9.4[y]	16.7 ± 6.8	20.9 ± 8.5	0.0001
Total skinfold thickness (mm)	52.1 ± 11.3	43.7 ± 22.2[t,u]	62.7 ± 24.5[y]	45.0 ± 17.8	58.9 ± 21.7	0.0001
Midarm circumference (cm)	26.9 ± 3.0[b]	24.6 ± 3.2[t,u]	29.5 ± 3.3[y]	26.2 ± 3.7	28.2 ± 3.4	0.0001
Midarm muscle circumference (cm)	22.8 ± 3.5[b]	21.2 ± 2.7[t,u]	25.1 ± 2.9	22.9 ± 3.7	24.0 ± 2.9	0.0001
Serum albumin level (g/dL)	4.5 ± 0.3[a,b,d]	4.1 ± 0.6[u]	4.1 ± 0.4[z]	3.8 ± 0.4[v]	4.5 ± 0.3	0.0001
nPNA (g/kg/day)	—	0.96 ± 0.21	0.82 ± 021	0.95 ± 0.3	1.01 ± 0.24	
Kt/V		1.45 ± 0.26		2.49 ± 0.78		
Dialysis vintage (months)	—	47.0 ± 38.2	—	43.1 ± 41.8		NS
Duration of follow-up posttransplantation (months)	—	—	—	—	69.3 ± 83.1	
Serum creatinine (mg/dL)	0.75 ± 0.14					
Creatinine clearance (ml/min)	—	—	19.7 ± 10.2	—	70.4 ± 22.4	
BUN clearance (ml/min)		—	10.4 ± 4.8	—	37.4 ± 13.9	
GFR estimation with MDRD formula (ml/min/1.73 m^2)	106.8 ± 19.8	—	15.9 ± 7.1	—	63.7 ± 18.2	

[a]Group 1 vs group 2; [b]group 1 vs group 3; [c]group 1 vs group 5; [d]group 1 vs group 4; [x]group 2 vs group 4; [y]group 3 vs group 4; [z]group 3 vs group 5; [t]group 2 vs group 3; [u]group 2 vs group 5; [v]group 4 vs group 5.

BMI = body mass index; BUN = blood urea nitrogen; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease study equation; nPNA, protein equivalent of total nitrogen appearance.

Table 3 Comparison of groups according to presence of PEW and surrogates of PEW

Features	Control group n (%)	Hemodialysis group n (%)	Predialysis group n (%)	Peritoneal dialysis group n (%)	Kidney transplantation group n (%)	P value
Body mass index ≥23 kg/m^2	18 (60)[a,d]	19 (63.3)[t]	26 (86.7)[b]	17 (56.7)[u]	25 (83.3)	0.025
Body fat ratio >10%	30 (100)	27 (90)	30 (100)	26 (86.7)	30 (100)	NS
Midarm muscle circumference >50%	24 (80)[z,y,d]	6 (20)[t,x,v]	24 (80)[b,c]	16 (53.3)	16 (53.3)	0.0001
Presence of PEW	0 (0)[z,y]	7 (23.3)[t,v]	1 (3.3)[b]	8 (26.7)[u]	0 (0)	0.0001

[a]Group 1 vs group 3; [b]group 3 vs group 4; [c]group 3 vs group 5; [d]group 1 vs group 5; [t]group 2 vs group 3; [u]group 4 vs group 5; [z]group 1 vs group 2; [y]group 1 vs group 4; [x]group 2 vs group 4; [v]group 2 vs group 5.
PEW = protein-energy wasting.

among peritoneal dialysis patients (r: –0.380, p: 0.037; r: 0.366, p: 0.047 respectively). We did not find any relationship between presence of PEW among peritoneal dialysis patients and serum ghrelin, resistin and neuropeptide Y levels.

Age of all of the groups was found to be negatively correlated with serum albumin levels, and creatinine clearance (r:–0.274, p: 0.001; r:–0.338, p: 0.008 respectively).

DISCUSSION

CKD is often characterized by wasting of muscle and fat mass, which has been defined as PEW, and is responsible for substantial worsening of patient outcome in terms of morbidity and mortality, mostly from cardiovascular events. In the evaluation of chronic hemodialysis patients with PEW, ghrelin (which is orexigenic hormone predominantly produced by the stomach) abnormalities: especially low levels of serum ghrelin levels were reported to contribute to anorexia, inflammation, and cardiovascular risk in hemodialysis patients, leading to worse outcome.[19] However, in our study, we did not find neither any difference in ghrelin levels of the groups nor any correlations between PEW and ghrelin levels. Instead, we found that ghrelin was negatively correlated with BMI and MAMC. A relationship between ghrelin and adipose tissue has been previously reported. Ghrelin was reported to stimulate adipogenesis and circulating ghrelin levels were reported to be reduced in obesity.[20] The mechanism underlying this observation might be negative influence of both glucose and insulin on ghrelin secretion.[21] In conclusion, ghrelin levels are influenced by many factors like nutritional status, BMI of the individual.

Opposite to total ghrelin, one of the two circulating forms of ghrelin: acylated ghrelin, which was thought to be the biologically active form of ghrelin,[22] were lower in predialysis, kidney transplant and peritoneal dialysis patients than control group in our study. These results were in accordance with other studies.[23] Kidneys are important sites for ghrelin and its metabolites clearance. Impairment of these organs might lead to increased levels of these peptides, in spite of our findings of low concentration of acylated ghrelin levels in patients with CKD. In our study, predialysis, transplant and peritoneal dialysis (PD) patients had higher BMI than those of hemodialysis and control groups. This might have had inhibitory effect on acylated ghrelin levels of these patients. Still, our results showing significant negative correlation of acylated ghrelin with creatinine clearance (predialysis and transplantation groups) are compatible with previous information. Circulating ghrelin levels increase after fasting and in clinical conditions like energy restriction, cachexia; and decrease with food intake and in clinical situations such as obesity.[24,25] Our data also showed that acylated ghrelin was negatively associated with MAMC.

Lower adiponectin levels are usually found in patients with high cardiovascular risk such as obesity, diabetes mellitus; higher levels are observed in another group with cardiovascular risk, namely CKD patients.[26] Elevated resistin levels were reported to be associated with the likelihood of CKD.[27] We also found that CKD patients except transplant patients had higher adiponectin and resistin levels than control group.

In this particular study, serum albumin levels were negatively correlated with only resistin and adiponectin. Both adiponectin and resistin were inversely correlated with creatinine clearance. It appears that high rather than low adiponectin predict increased mortality in CKD patients.[26] It was just hypothesized that in uremic millieu, high adiponectin levels reflect PEW, which is present in approximately 20–50% of the maintenance dialysis patients. Likewise, we observed that 23% of hemodialysis

Table 4 Adipocytokine measurements of the groups (mean ± standard deviation)

Variables	Control group	Hemodialysis group	Predialysis group	Peritoneal dialysis group	Kidney transplantation group	P value
Acylghrelin level (pg/mL)	5.87 ± 4.40[a,b,c]	3.80 ± 2.80	2.68 ± 3.18	1.89 ± 1.83	2.23 ± 1.92	0.003
Ghrelin (ng/mL)	92.25 ± 18.33	93.14 ± 29.86	78.66 ± 26.08	85.73 ± 21.94	79.66 ± 29.05	NS
Leptin (ng/mL)	13.62 ± 11.86	20.82 ± 31.74	26.95 ± 31.63	18.22 ± 26.85	11.53 ± 13.61	NS
Adiponectin (ng/mL)	17,627.6 ± 11421.1[d,b]	49,665.7 ± 35,010.7[v,u]	34,626.5 ± 33,635.0[z]	75,646.3 ± 56721.1[x]	15,242.3 ± 10,306.7	0.0001
Resistin (ng/mL)	4.71 ± 3.44[d,a,b]	16.12 ± 4.93[t,u]	11.65 ± 5.77[z,y]	17.82 ± 6.03[x]	6.91 ± 2.11	0.0001
Neuropeptide *y* (pg/mL)	606.34 ± 296.51[b,c]	763.90 ± 241.67[u,v]	636.82 ± 350.39[z,y]	239.67 ± 294.16	412.66 ± 319.91	0.0001

[a]Group 1 vs group 3; [b]group 1 vs group 4; [c]group 1 vs group 5; [d]group 1vs group 2; [t]group 2 vs group 3; [u]group 2 vs group 5; [z]group 3 vs group 4; [y]group 3 vs group5; [x]group 4 vs group 5; [v]group 2 vs group 4.

and 26.7% of PD patients had PEW, which was found to be positively associated with adiponectin and resistin. As far as we know, this study is the first one to show the linear association of resistin and adiponectin with PEW among dialysis patients.

Our data also revealed that acylated ghrelin was positively correlated with adiponectin, ghrelin and neuropeptide Y levels. It is logical because both ghrelin and adiponectin were inversely correlated with BMI and both acylated ghrelin and adiponectin were inversely correlated with creatinine clearance. Krzyzanowska-Swiniarska B and colleagues also reported positive association of adiponectin with ghrelin in obese women without insulin resistance.[28] The gastric hormone ghrelin stimulates appetite by activating the neuropeptide Y (which is one of the most important stimulants of food intake) expressing neurons in arcuate-nucleus region of the hypothalamus.[29] Linear correlation of acylated ghrelin with neuropeptide Y and low levels of neuropeptide Y in parallel with acylated ghrelin among PD and transplant patients is expected.

Some other studies had stressed the negative correlation between leptin (which is anorexigenic peptide predominantly produced by adipocytes) and GFR.[30] Even though in our study, all of the groups had statistically similar leptin levels, we found significant positive correlations between leptin and body fat ratio, BMI and significant negative correlation between leptin and GFR similar to previous studies.[30] Leptin, like ghrelin, acylated ghrelin and neuropeptide Y did not seem to have any association with PEW of hemodialysis patients according to our study. But among peritoneal dialysis patients, significant negative correlations with leptin and PEW were observed.

We also found that duration of follow-up posttransplantation was inversely correlated with leptin, neuropeptide Y, adiponectin, and acylated ghrelin. No information related to effects of adipokines on posttransplantation follow-up duration was found in the literature.

In conclusion, advanced CKD is associated with dysregulations of adipocytokines (resistin, adiponectin). CKD patients except transplant patients had higher adiponectin and resistin levels than control group. Twenty-three percent of hemodialysis 26.7% of PD patients had PEW. PEW was positively correlated with resistin and adiponectin. To form strategies to prevent PEW of CKD patients, pathogenesis should be understood and alteration of adipokines might be important in genesis of PEW in CKD patients. Further research should be needed to enlighten relationship between these peptides and PEW of maintenance dialysis patients.

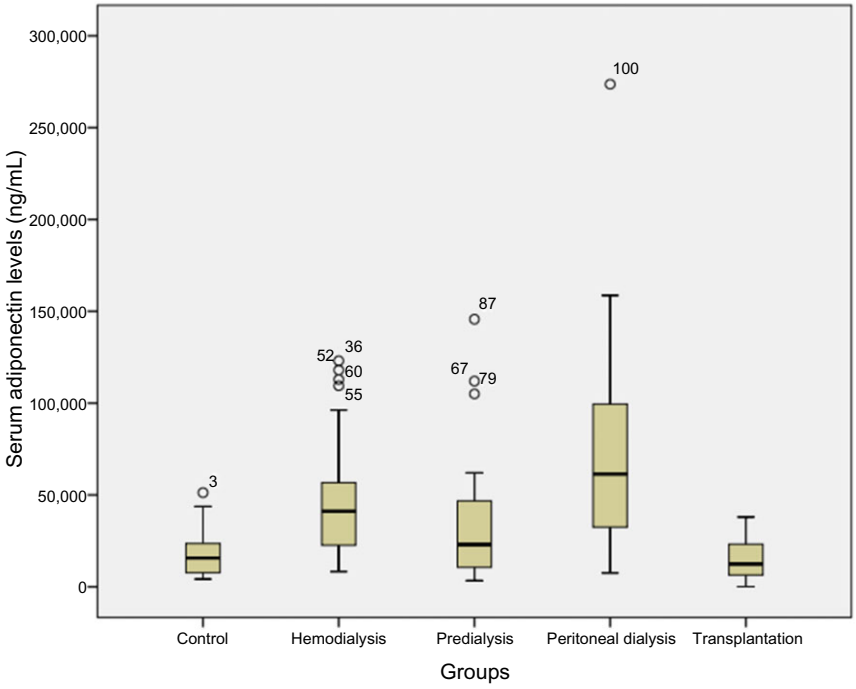

Figure 1 Bar plot view of adiponectin levels of the groups.

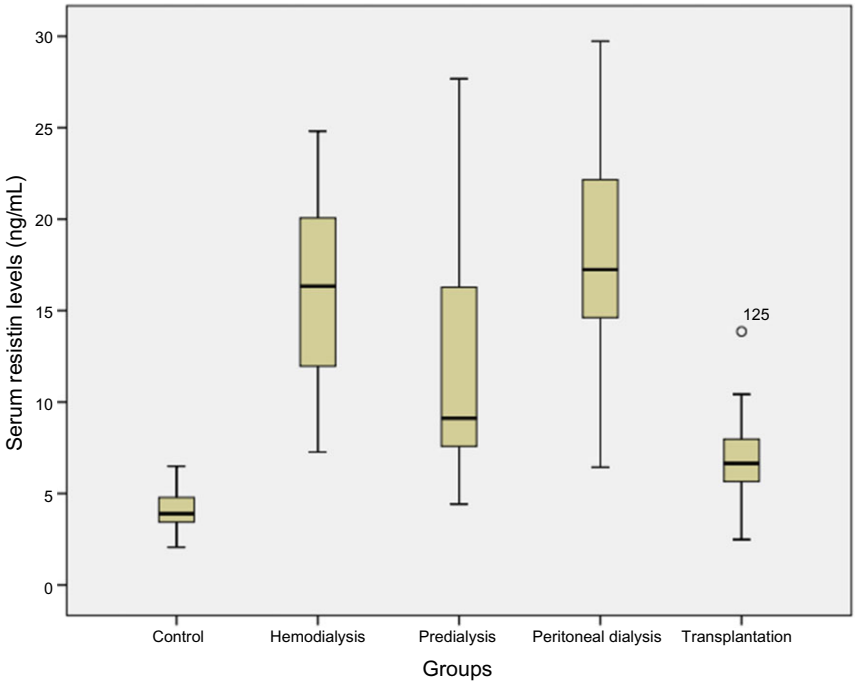

Figure 2 Bar plot view of resistin levels of the groups.

Table 5 Coefficient of variation (in %) for the measurement of adipocytokines of the groups

Variables	Control	Hemodialysis	Groups predialysis	Peritoneal dialysis	Kidney transplantation
Ghrelin (ng/mL)	20.2	31.5	33.2	25.6	36.5
Resistin (ng/mL)	23.8	30.5	49.6	33.9	30.4
Neuropeptide y (pg/mL)	49.7	31.6	55.0	122.7	77.5
Leptin (ng/mL)	67.7	144.6	117.4	147.3	118.1
Adiponectin (ng/mL)	66.3	71.0	97.1	75.0	67.6
Acylghrelin level (pg/mL)	70.6	76.7	118.5	96.8	86.3

Table 6 Significant correlations of adipocytokines

Variable	Ghrelin	Leptin	Neuropeptide Y	Resistin	Adiponectin	Acylated-ghrelin
Body mass index	r: –0.195 p: 0.017	r: 0.540 p: 0.0001			r: –0.271 p: 0.001	
Midupper arm muscle circumference	r: –0.179 p: 0.029					r: –0.340 p: 0.003
Midupper arm muscle circumference of higher than 50th percentile		r: 0.422 p: 0.0001		r: –0.259 p: 0.001	r: –0.226 p: 0.005	
Acylated-ghrelin	r: 0.318 p: 0.005		r: 0.304 p: 0.008			
Duration of follow-up posttransplantation		r: –0.413 p: 0.023	r: –0.459 p: 0.011		r: –0.441 p: 0.015	r: –0.575 p: 0.025
Total skinfold thickness		r: 0.727 p: 0.0001			r: –0.243 p: 0.003	
Presence of body fat ratio of more than 10% of body weight		r: 0.224 p: 0.006		r: –0.167 p: 0.041		
nPNA		r: –0.298 p: 0.002				
Serum albumin level				r: –0.441 p: 0.001	r: –0.368 p: 0.0001	
Presence of PEW				r: 0.267 p: 0.001	r: 0.349 p: 0.0001	
Creatinine clearance				r: –0.529 p: 0.0001	r: –0.535 p: 0.0001	r: –0.365 p: 0.047
Adiponectin level				r: 0.431 p: 0.0001		r: 0.271 p: 0.019
GFR with MDRD Formula (mL/min/1.73 m^2)		r: –0.262 p: 0.044				

GFR, glomerular filtration rate; MDRD, modification of diet in renal disease study equation; nPNA, protein equivalent of total nitrogen appearance; PEW = protein-energy wasting.

Limitations of this study

Groups were not homogenous with respect to age and BMI. Acylghrelin levels were only studied in half of the groups because of insufficiency of kits. Insulin sensitivity of patients were not explored.

ACKNOWLEDGMENT

We thank very much to our hemodialysis and peritoneal dialysis nurses Asiye Aydin and Meryem Bakkaloglu for their careful and devoted follow up of patients.

Manuscript received April 2013; revised June 2013.

REFERENCES

1 Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy

wasting in acute and chronic kidney disease. *Kidney Int*. 2008; **73**:391–398.
2 Kalantar-Zadeh K, Kuwae N, Wu DY, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr*. 2006; **83**:202–210.
3 Carrero JJ, Chmielewski M, Axelsson J, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr*. 2008; **27**:557–564.
4 Bonanni A, Mannucci I, Verzola D, et al. Protein-energy wasting and mortality in chronic kidney disease. *Int J Environ Res Public Health*. 2011; **8**:1631–1654.
5 Niemczyk S, Romejko-Ciepielewska K, Niemczyk L. Adipocytokines and sex hormone disorders in patients with chronic renal failure (CRF). *Endokrynol Pol*. 2012; **63**:148–155.
6 Mak RH, Cheung WW. Is ghrelin a biomarker for mortality in end stage renal disease. *Kidney Int*. 2011; **79**:697–699.
7 Daugirdas JT. Second generation logarithmic estimates of single pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol*. 1993; **4**:1205–1213.
8 Lightfoot BO, Caruana RJ, Mulloy LL, Fincher ME. Simple formula for calculating normalized protein catabolic rate (nPCR) in hemodialysis (HD) patients (abstract). *J Am Soc Nephrol*. 1993; **4**:363–363.
9 Tzamaloukas AH, Murata GH, Malhotra D, Sena P, Patron A. Urea kinetic modeling in continuous peritoneal dialysis patients. Effect of body composition on the methods for estimating urea volume of distribution. *ASAIO J*. 1993; **39**:M359–M362.
10 Keshaviah PR, Nolph KD. Protein catabolic rate calculations in CAPD patients. *ASAIO Trans*. 1991; **37**:M400–M402.
11 Van Acker BA, Koomen GC, Kopman MG, de Waart DR, Arisz L. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet*. 1992; **340**:1326–1329.
12 Levey AS, Bosch JP, Lewis JB, Grene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; **130**:461–470.
13 Dombros N, Dratwa M, Feriani M, et al. European Best Practice Guidelines for peritoneal dialysis.The initiation of dialysis. *Nephrol Dial Transplant*. 2005; **20**(Suppl 9): 3–7.
14 Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int*. 1985; **27**:58–65.
15 Fouque D, Vennegoor M, Wee PT, et al. EBPG Guideline on nutrition. *Nephrol Dial Transplant*. 2007; **22**(Suppl 2): 45–87.
16 Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: Emasurements on 481 men and women aged from 16–72 yeras. *Br J Nutr*. 1974; **32**:77–97.
17 WHO. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000; **894**:1–253.
18 Bishop CW, Bowen PE, Ritchey SJ. Norms for nutritional assessment of American adults for upper arm anthropometry. *Am J Clin Nutr*. 1981; **34**:2530–2539.
19 Carrero JJ, Nakashima A, Qureshi AR, et al. Protein-energy wasting modifies the association of ghrelin with inflammation, leptin, and mortality in hemodialysis patients. *Kidney Int*. 2011; **79**:749–756.
20 Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. *Diabetes*. 2001; **50**:707–709.
21 Ukkola O. Ghrelin and insulin metabolism. *Eur J Clin Invest*. 2003; **33**:183–185.
22 Date Y, Kojima M, Hosoda H, et al. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology*. 2000; **141**:4255–4261.
23 Oner-Iyidogan Y, Gurdol F, Kocak H, et al. Appetite-regulating hormones in chronic disease patients. *J Ren Nutr*. 2011; **21**:316–321.
24 Shiiya T, Nakazato M, Mizuta M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. *J Clin Endocrinol Metab*. 2001; **87**:240–244.
25 Yoshimoto A, Mori K, Sugawara A, et al. Plasma ghrelin and desacyl ghrelin concentrations in renal failure. *J Am Soc Nephrol*. 2002; **13**:2748–2752.
26 Chudek J, Adamczak M, Nieszporek T, Wiecek A. The adipose tissue as an endocrine organ—a nephrologists' perspective. *Contrib Nephrol*. 2006; **151**:70–90.
27 Kawamura R, Doi Y, Osawa H, et al. Circulating resistin is increased with decreasing renal function in a general Japanese population: The Hisayama Study. *Nephrol Dial Transplant*. 2010; **25**:3236–3240.
28 Krzyzanowska-Swiniarska B, Kempa A, Miazgowski T, Pilarska K. Serum acylated ghrelin, adiponectin and leptin levels in normal-weight and obese premenopausal women. *Horm Metab Res*. 2007; **39**:835–839.
29 Mak RH, Cheung W, Cone RD, Marks DL. Orexigenic and anorexigenic mechanisms in the control of nutrition in chronic kidney disease. *Pediatr Nephrol*. 2005; **20**:427–431.
30 Daschner M, Tonshoff B, Blum WF, 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**:1074–1079.