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Association of Serum Adropin Levels with Nutritional Status and Lipid Profile in Patients with Kidney Failure with Replacement Therapy

Gamze Yurtdaş Depboylu[1*], Nilüfer Acar Tek[2], Burcu Deniz Güneş[3], Özge Mengi Çelik[4], Gizem Özata Uyar[2], Ayşe Derya Bayazıt[2], Emre Yaşar[5], Yasemin Erten[5]

Abstract

Objective. This study aimed to determine serum adropin levels and to examine the relationship of serum adropin levels with nutritional status and lipid profile in patients with kidney failure with replacement therapy (KFRT).

Methods. The study consisted of 88 subjects, including 30 patients treated with hemodialysis (HD), 29 patients treated with peritoneal dialysis (PD), and 29 patients who had undergone kidney transplantation (TX). The study included assessing anthropometric measurements, handgrip strength, bioelectrical impedance analysis, malnutrition-inflammation score, dietary intake, resting energy expenditure, and biochemical parameters. The patients' food consumption was recorded for three days. The malnutrition-inflammation score (MIS) was calculated to assess the patients' nutritional status. Blood samples were collected for serum adropin and other biochemical parameters.

Results. Adropin levels were significantly higher in the TX group when compared to the HD group. Patients with low adropin levels had higher MIS, serum ferritin, and lower low-density lipoprotein-cholesterol (LDL-C) and total cholesterol (total-C) levels. Serum adropin levels were negatively correlated with the MIS and positively correlated with total-C, LDL-C, and HDL-C levels. Multiple linear regression analyses showed that the MIS ($\beta = -0.25$, p=0.038) and LDL-C level ($\beta = 0.29$, p=0.007) were associated with serum adropin.

Conclusions. Adropin may be considered as a new marker of nutritional status and possibly plays a role in the pathophysiological mechanisms and complications of patients with KFRT.

Keywords
Adropin; Malnutrition; Chronic Kidney Disease; Lipid Profile; Kidney Failure with Replacement Therapy

[1] *Department of Nutrition and Dietetics, Faculty of Health Sciences, Izmir Katip Celebi University, Izmir, Turkey*
[2] *Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Turkey*
[3] *Department of Nutrition and Dietetics, Faculty of Health Sciences, Adnan Menderes University, Aydin, Turkey*
[4] *Department of Nutrition and Dietetics, Faculty of Health Sciences, Health Science University, Ankara, Turkey*
[5] *Department of Nephrology, Faculty of Medicine, Gazi University, Ankara, Turkey*
***Corresponding author**: gmzyurtdas@hotmail.com

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with a prevalence of approximately 10% [1]. Kidney failure (KF), which is the last stage of CKD, is defined as a glomerular filtration rate (GFR) of less than 15 mL/min. Numerous diseases, including diabetes mellitus (DM), hypertension, vascular disease, glomerular disease, etc., can cause KF [2]. Patients with KF require kidney replacement therapy (dialysis or kidney transplant) [2].

Protein-energy malnutrition and lipid abnormalities are common problems in patients with CKD and are associated with high mortality and morbidity [3, 4]. The exact mechanism of these complications is not clearly understood. Recently, it has been suggested that newly discovered myokines may be associated with these complications [5, 6]. Adropin is a newly discovered myokine that is expressed mainly in the liver and brain. Additionally, it is found in the lungs, heart, kidney, and muscles [6, 7]. This

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bioactive protein weighs 4499.9 Da and contains 76 amino acid chains. First discovered in mice by Kumar *et al.* [8] in 2008, this peptide is encoded by the energy homeostasis-associated gene (ENHO). Adropin has been shown in studies to have a wide variety of effects. The most obvious of these effects is maintaining energy homeostasis by regulating glucose and lipid metabolism [8, 9]. In recent studies, low adropin levels have been shown to be associated with coronary artery disease, obesity, type 2 DM, and insulin resistance [10–12]. Yuan *et al.* [11] showed that serum adropin levels were negatively associated with body mass index (BMI), waist-to-hip ratio (WHR), and triglyceride and positively associated with high-density lipoprotein cholesterol (HDL-C). Erman *et al.* [12] found that serum adropin levels were inversely related to waist circumference, BMI, diastolic blood pressure, insulin, and fasting glucose. It has been reported that adropin may be a protective agent against metabolic syndrome [13]. Adropin levels were found to be negatively correlated with albumin concentrations, lean tissue mass, body mass, and total intracellular (ICW) and extracellular water (ECW) in CKD patients [6]. Based on these findings, it has been suggested that adropin may be a new nutritional status marker in this patient group [6].

Data on myocyte-secreted proteins are of clinical importance, especially in KF patients, as malnutrition and an impaired lipid profile are important predictors of mortality [14]. In the literature, there is no study evaluating the association of adropin levels with malnutrition and lipid profile in patients with KF with replacement therapy (KFRT).

This study aimed to determine serum adropin levels in patients with KFRT and to examine the relationship of serum adropin levels with nutritional status and lipid profile.

Materials and Methods

Study Desing and Population

This cross-sectional study was conducted in a nephrology outpatient clinic and dialysis units of Gazi University Hospital in Ankara, Turkey (October 2019 - January 2020). A total of 88 patients, including 30 patients treated with hemodialysis (HD), 29 patients treated with peritoneal dialysis (PD), and 29 patients who had undergone kidney transplantation (TX) at least six months earlier, were included in the study. The TX group patients were receiving maintenance immunosuppression therapy (combined with everolimus/tacrolimus/cyclosporine, mycophenolate mofetil/mycophenolic acid, and prednisolone) according to our protocols. Patients in the HD group were receiving thrice-weekly dialysis therapy (4 hours per session).

Exclusion criteria were as follows: acute or chronic liver failure, hematological disorders, active autoimmune disease or neoplasm, thyroid dysfunction (hypo- and hyperthyroidism), cognitive impairment, history of acute infection in the past seven days, patients receiving less than three sessions per week and/or those receiving hemodialysis treatment for less than three months, pregnant and lactating women, those under 18 years old and over 90 years old. These criteria were applied because they have the potential to affect nutritional status. Non-Interventional Clinical Research Ethics Committee approval was obtained for this study (number: 35).

Anthropometric Measurements

Research dieticians took anthropometric measurements in the morning, at least eight hours following the end of the fast. Using an electronic scale (Medical Scale DR-Mod 85) with a sensitivity of 0.1 kg, the patients' after-dialysis body weights (dry weight) were determined [15]. BMI was calculated according to the formula: $BMI = [after-dialysis\ weight(kg)/height(m^2)]$.

The conicity index (Ci), which measures fat accumulation in the belly as the body divergence from a cylindrical shape towards a double cone shape, was used to measure the amount of abdominal fat deposition. The Ci was calculated using the equation defined by Valdez [16]: $Ci = [Waist\ circumference/[0.109 \times \sqrt{(weight/height)}]$. The body adiposity index (BAI) was calculated as proposed by Bergman *et al.* [17]:

"$BAI = hip\ circumference(cm)/height(m)^{\frac{1}{2}} - 18$".

Handgrip Strength

Handgrip strength was measured by a dynamometer (T.K.K. 5401). The measurement was repeated four times with the maximum tension, and the mean values were recorded. The measurements were performed from non-fistula arm in the HD group with arteriovenous fistula.

Bioelectrical Impedance Analysis

Body composition was assessed using bioelectrical impedance analyzer (InBody S10, Korea), which provides six distinct frequency impedance measurements and three distinct frequencies of phase angle measurement for each of five segments. Water volumes (ECW and ICW), the proportion of ECW to total body water, and the history of body water status are hydration-related outputs. Fat-free mass index (FFMI) was calculated according to the following equation: $FFMI = fat-freemass[kg]/(height[m])^2$ [18].

Malnutrition-Inflammation Score (MIS)

The MIS was used to assess the patients' nutritional status. The MIS is a semi-quantitative scale evaluating ten components, including weight changes, BMI, serum albumin level, serum total iron-binding capacity (TIBC), dietary intake, functional capacity, disease state, physical exam (muscle wasting, loss of subcutaneous fat), and gastrointestinal symptoms. Each of the ten criteria is graded on a scale from "0-normal" to "3-most severe" in four distinct ways. The total of 10 separate MIS criteria run from 0 (normal) to 30 (severe malnutrition). High scores indicate a greater risk of inflammation and malnutrition [19].

Dietary Intake

Dietary intake was assessed by using three-day food records by the research dietician (one dialysis day and two non-dialysis days for the HD groups). Dietary energy and nutrients were calculated using BeBiS software.

Resting Energy Expenditure (REE)

After at least eight hours of fasting, REE measurements were carried out using an indirect calorimeter. Patients had been told to eat regularly and refrain from engaging in strenuous activity for the 24 hours before the measurement. Patients took a 15-minute break in a sitting position before the test. Prior to each measurement, the equipment was automatically calibrated. To measure oxygen consumption (VO_2; ml/min), a sterile mask that covers the mouth and nose was utilized. In a peaceful, thermoneutral ($22-24^{\circ}C$) setting, patients were measured in a supine position while resting in an immobile state.

Biochemical Measurements

Fasting blood samples were obtained from all patients. Albumin, fasting blood glucose, TIBC, ferritin, low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), total cholesterol (total-C), uric acid, HDL-C, creatinine, and triglyceride levels were measured using the clinical chemistry autoanalyzer and original kits. The GFR was calculated with the CKD-EPI equation based on creatinine [20]. Serum interleukin (IL) -6 levels were measured by using IMMULITE 2000 with the chemiluminescence immunoassay technique.

The following formula was used to determine the atherogenic index: (TG/HDL-C) log10 [21]. Some lipid indices were calculated, including non-HDL-C (total-C minus HDL-C) and LDL-C/HDL-C [22].

Serum adropin levels were evaluated in the blood samples taken from patients after eight hours of fasting. Blood samples were centrifuged, and then serum samples were stored at $-80^{\circ}C$ until laboratory analyses. Serum adropin levels were measured by using a commercial enzyme-linked immunosorbent assay (ELISA) kit (USCN-SEN251 Hu) according to its original method. The detection range of the assay was 2-0.0312 ng/mL. The minimum detectable dose of adropin was typically less than 0.0133 ng/mL. There is no cut-off value for serum adropin levels. Patients were categorized into low (< 0.98 ng/mL/day) and high (≥ 0.98 ng/mL) adropin groups based on mean adropin values.

Statical Analysis

SPSS 22.0 software was used to perform all statistical analyses. Categorical data were presented as number (n) and percentage (%). The Shapiro-Wilk test was used to assess the conformity of continuous variables to the normal distribution. In normally distributed data, mean and standard deviation (SD) values were calculated. The three groups were compared using the one-way ANOVA test. The Student's t-test was used to compare groups with low and high serum adropin levels. Pearson correlation analysis was used to appraise correlation levels between adropin and various parameters. Linear regression was carried out to determine the association between adropin and related factors. A 2-sided p-value of < 0.05 was considered as statistically significant.

Results

Table 1 summarizes the demographic and clinical features of the subjects. Most subjects in the HD and TX groups were men, most patients in the PD groups were women. Patients had hypertension (58.0%), cardiovascular disease (27.3%), and DM (20.5%) as concomitant conditions. In terms of age, sex, and comorbidities, there were no statistically significant differences between the three groups. Adropin levels were significantly greater in the TX group (1.0 ± 0.14) compared to the HD group (0.8 ± 0.18) ($p < 0.001$) (Table 1). There were no significant differences in the levels of total-C and LDL-C in all the groups. The MIS score was significantly lower in the TX group compared to the PD and HD group ($p < 0.001$). There were no significant differences in terms of the MIS scores between the HD and PD groups. Handgrip strength was higher in the TX group compared to the PD group. There was a significant difference between the groups in terms of albumin values of patients ($p < 0.001$). HDL-C levels were significantly higher in the TX group than in the HD group. In terms of average energy and protein intake, there was no statistical difference between the groups.

Table 1. Comparison of demographic and clinical characteristics of participants.

	HD (n=30) M±SD	PD (n=29) M±SD	TX (n=29) M±SD	p-value
Demographic variables				
Age (years)	45.4±11.34	51.2±12.91	45.0±8.87	0.066
Men (n, %)	21 (70.0)	13 (44.8)	16 (55.2)	0.145
Cardiovascular disease (n, %)	6 (20.0)	9 (31.0)	9 (31.0)	0.876
DM (n, %)	6 (20.0)	3 (10.3)	9 (31.0)	0.142
Hypertension (n, %)	13 (43.3)	21 (72.4)	17 (63.0)	0.364
Anthropometric measurements				
BMI (kg/m^2)	25.4±4.94	26.6±4.14	26.4±4.49	0.556
WC (cm)	95.2±17.24	93.7±12.41	98.0±10.50	0.480
WHR	0.9±0.09	0.9±0.07	0.9±0.05	0.593
Mid upper circumference (cm)	29.0±4.80	28.0±3.66	29.8±3.16	0.223
Ci	1.3±0.13	1.3±0.09	1.3±0.03	0.243
BAI	27.9±5.20	31.3±6.09	29.9±6.97	0.087
Handgrip strength (kg)	27.4±10.24[a]	21.8±8.02[b]	30.7±12.37[c]	**0.006, c>b**

Table 1 continues on the next page.

Table 1 (Continued).

	HD (n=30) M±SD	PD (n=29) M±SD	TX (n=29) M±SD	p-value
Body composition				
ICW (L)	23.9±5.04	22.4±5.07	23.7±5.20	0.512
ECW (L)	14.5±2.97	13.8±3.08	14.4±2.96	0.631
TBW (L)	38.5±7.97	36.3±8.14	38.1±8.13	0.555
Phase angle (∘)	6.2±1.14	6.0±0.95	6.3±0.93	0.584
Fat-free mass (kg)	52.5±10.79	49.5±11.08	51.9±11.12	0.586
FFMI (kg/m^2)	17.9±2.24	18.8±2.38	18.4±2.30	0.364
Body fat (%)	26.5±11.44	26.5±11.44	29.9±8.79	0.448
Laboratory parameters				
Glucose (mg/dL)	101.8±38.53	98.1±37.99	98.6±21.89	0.833
Albumin (mg/dL)	4.1±0.37^a	3.6±0.37^b	4.2±0.27^c	**<0.001, c>b, a>b**
Adropin (ng/mL)	0.8±0.18^a	1.0±0.25^b	1.0±0.14^c	**0.002, c>a**
Total-C (mg/dL)	177.7±52.63	214.6±76.89	216.0±63.05	0.055
Triglyceride (mg/dL)	181.1±172.71	220.3±191.60	207.0±2.96	0.911
HDL-C (mg/dL)	38.1±9.19^a	45.0±5.07^b	52.6±19.86^c	**<0.001, c>a**
LDL-C (mg/dL)	104.2±36.51	125.5±43.48	121.9±44.80	0.159
LDL-C/HDL-C	2.7±0.95	2.8±0.85	2.4±0.96	0.304
Creatinine (mg/dL)	8.1±2.37^a	8.1±2.95^b	1.1±0.33^c	**<0.001, b>c, a>c**
Atherogenic index	0.6±0.25	0.5±0.34	0.5±0.32	0.165
Dietary intake				
Energy intake (kcal/kg/d)	23.3±6.37	23.5±8.08	22.1±6.89	0.722
Protein intake (g/kg/d)	0.8±0.23	0.8±0.23	0.7±0.23	0.443
MIS	6.5±2.95^a	5.7±3.32^b	2.4±2.17^c	**<0.001, b>c, a>c**
REE (kcal)	1756.0±412.2^a	1490.4±305.3^b	1715.3±444.1^c	**0.023, a>b**

Notes: a p-value of less than 0.05 was considered statistically significant. Data are expressed as mean (M)±standard deviation (SD). Each variable is presented with a different letter (a, b, c) in variables with statistically significant difference between groups.
Abbreviations: BMI - body mass index, C - cholesterol, HDL-C - high-density lipoprotein cholesterol, WC - waist circumference, WHR - waist-to-hip ratio, Ci - conicity index, BAI - body adiposity index, MIS - malnutrition-inflammation score, ECW - extracellular water, ICW - intracellular water, TBW - total body water, FFMI - fat-free mass index, REE - resting energy expenditure.

Serum adropin levels were determined to be high or low using a cut-off serum adropin level of 0.98 ng/mL. Patients with low adropin levels had higher MIS scores, higher ferritin, and lower LDL-C, total-C (Table 2).

The correlation of serum adropin levels with various factors is presented in Table 3. Serum adropin levels were strong and negatively correlated with the MIS score; they were positively correlated with total-C (strong), LDL-C (strong), and HDL-C (weak) in all patients. In patients who had undergone kidney transplantation, there was a strong negative relationship between serum adropin levels and fat mass percentage (%). In patients treated with PD, there was a strong positive correlation between adropin levels and total-C and LDL-C.

Table 4 shows multiple linear regression to evaluate the relationship between adropin and associated covariates. After multivariable adjustment, the MIS ($\beta = -0.25$, $p = 0.038$), and LDL-C level ($\beta = 0.29$, $p = 0.007$) were associated with serum adropin.

Discussion

To the best of our knowledge, the present study is the first to evaluate the association of serum adropin levels with nutritional status and lipid profile in patients with KFRT. This study demonstrated that malnutrition and LDL-C level were associated with serum adropin.

Malnutrition is a very common complication in patients with KFRT due to metabolic and hormonal irregularities, systemic inflammation, inadequate nutrient intake, and adverse effects of kidney replacement therapy [23]. The prevalence of malnutrition among patients treated with dialysis is reported to be between 52.9% and 61.2% [24, 25]. However, improvement in clinical and nutritional status has been demonstrated in kidney transplant patients [26]. In one study, it was determined that malnutrition index score decreased in kidney transplant patients six months after transplantation compared to that before transplantation [26]. In this study, the patients' malnutrition status was evaluated with the MIS, and following the literature, it was found that the MIS score was high in the HD group and low in TX patients. Handgrip strength, which is associated with lean body mass [27] was found to be higher in transplant patients in parallel with the results of the MIS (Table 1).

Adropin is a new peptide hormone that is encoded by the ENHO gene, and its expression is influenced by body fat composition, energy status, and diet [8, 9]. Recent research has suggested that adropin should be investigated in detail as a possible marker of cachexia in patients with CKD [28]. In this study, patients with low adropin levels had higher MIS. Moreover, low adropin levels were found to be associated with malnutrition when adjusted for age, gender, BMI, and CKD groups (Table 4). Consistent with these results, the MIS and serum adropin levels were found to be inversely related in hemodialysis patients [5]. Similarly, an inverse relationship was found between serum adropin level and body mass, BMI, and albumin levels

Table 2. Anthropometric and biochemical characteristics in low and high serum adropin subgroups.

	Low adropin (n=45)	High adropin (n=43)	p-value
Anthropometric measurements			
BMI (kg/m²)	26.3±5.11	26.0±3.88	0.727
BAI	30.0±6.71	29.3±5.74	0.574
Ci	1.3±0.10	1.3±0.10	0.316
Handgrip strength (kg)	26.5±10.79	26.8±11.09	0.891
Body composition			
Body fat (%)	29.3±11.57	27.6±8.55	0.436
Fat-free mass (kg)	51.9±10.19	50.5±11.80	0.571
FFMI (kg/m^2)	18.1±2.37	18.6±2.24	0.447
Phase angle (○)	6.3±0.94	6.0±1.05	0.190
Laboratory parameters			
TIBC (µg/dL)	200.2±67.58	233.3±73.64	**0.030**
Albumin (mg/dL)	4.0±0.41	4.0±0.44	0.521
Glucose (mg/dL)	100.5±34.33	97.32±32.85	0.658
Ferritin (mg/dL)	418.6±397.31	257.2±295.79	**0.007**
CRP (mg/dL)	8.4±10.65	7.7±8.65	0.738
IL-6 (pg/dL)	9.2±15.24	6.3±4.85	0.251
LDL-C (mg/dL)	103.6±35.07	130.5±44.93	**0.002**
Triglyceride (mg/dL)	184.6±142.76	220.5±170.59	0.288
HDL-C (mg/dL)	43.9±18.80	46.4±10.74	0.442
Non-HDL-C (mg/dL)	140.2±51.77	174.6±70.08	**0.011**
LDL-C/HDL-C	2.5±0.95	2.8±0.89	0.131
Total-C (mg/dL)	184.1±53.31	221.0±73.58	**0.009**
Atherogenic index	0.56±0.33	0.59±0.28	0.626
Dietary intake			
Energy intake (kcal/kg/d)	23.1±7.07	22.8±7.18	0.856
Protein intake (g/kg/d)	0.8±0.24	0.7±0.21	0.580
MIS	5.6±3.25	4.2±3.34	**0.045**
REE (kcal)	1630.9±417.78	1679.2±394.8	0.579

Notes: low adropin <0.98 ng/mL; high adropin ≥0.98 ng/mL.
Abbreviations: TIBC – total iron-binding capacity, C – cholesterol, REE – resting energy expenditure, MIS – malnutrition inflammation score, FFMI – fat-free mass index, BMI – body mass index, BAI - body adiposity index, Ci – conicity index, LDL – low-density lipoprotein, HDL - high-density lipoprotein, IL-6: interleukin-6, CRP – C-reactive protein (mg/dL).

in KF patients [6]. It has been stated that cachexia and accompanying muscular atrophy in patients with KF may affect adropin levels [6]. A recent study has suggested that adropin may have protective effects on inflammation and chronic kidney damage progression [29]. In this study, although there was no significant relationship between inflammation parameters and adropin, it is noteworthy that CRP and IL-6 levels remained high in low adropin levels (Table 2). Adropin is also known to show a wide range of potential links with the types of macronutrients in dietary intake [30]. In this context, it could be hypothesized that malnutrition could be one of the causes of adropin down-regulation in patients with KFRT. In addition, the inverse relationship between lean body mass and adropin levels supports this hypothesis.

Adropin levels in the TX group were significantly higher than in the HD group ($p < 0.001$). There were no significant differences in the levels of adropin in the HD and PD groups (Table 1). Consistent with this study, Kałużna *et al.* [6] found that there were no differences in the levels of adropin between patients treated with HD and PD and healthy subjects. Liu *et al.* [31] showed that patients treated with HD had considerably lower serum adropin concentrations than healthy controls. In another study, it was shown that adropin levels were similar in patients treated with HD, TX, and PD [28]. Different methodologies used for measuring adropin levels might be the causative factor of the contradictory results in these studies. Differences in adropin concentrations in patients with KF were expected because of the kidney impairment itself, as well as malnutrition and concomitant changes in body composition. In this study, in line with the results mentioned above, adropin elevation in the TX groups can be explained by the lower MIS score compared to dialysis patients. Malnutrition in patients treated with HD could be the possible reason for low adropin level in patients treated with HD. Taken together, these findings suggest that adropin is possibly regulated by nutritional status.

In this study, no correlation was shown between serum adropin levels and BMI, anthropometric measurements, and body fat. These results are consistent with the results of other studies [32, 33]. On the other hand, it has been shown that serum adropin levels are positively correlated with BMI in patients with heart failure [34]. However, numerous studies have revealed that obesity is negatively associated with adropin levels, implying that higher body fat percentages likely have an adverse effect on circulating adropin levels [35, 36]. This study showed that serum adropin levels were significantly and negatively correlated with the fat mass percentage in the TX group (Table 3).

Table 3. Correlation of serum adropin levels with anthropometric and biochemical characteristics.

	All patients (n=88)		HD (n=30)		PD (n=29)		TX (n=29)	
	r	p	r	p	r	p	r	p
Anthropometric measurements								
BMI (kg/m^2)	0.03	0.782	0.21	0.296	−0.19	0.315	−0.08	0.691
WC (cm)	0.99	0.360	0.17	0.357	−0.05	0.808	−0.02	0.900
WHR	0.10	0.360	0.14	0.468	−0.05	0.805	0.03	0.871
Handgrip strength (kg)	0.09	0.456	−0.23	0.202	0.04	0.843	0.23	0.239
Body composition								
Body fat (%)	−0.09	0.407	0.23	0.250	−0.33	0.083	−0.48	**0.009**
Fat-free mass (kg)	0.12	0.269	−0.15	0.433	0.17	0.382	−0.12	0.554
FFMI (kg/m^2)	0.21	**0.048**	0.02	0.935	0.33	0.086	0.26	0.171
ICW (L)	0.12	0.276	−0.14	0.464	0.18	0.356	0.29	0.126
ECW (L)	0.12	0.257	−0.13	0.507	0.18	0.349	0.34	0.069
TBW (L)	0.12	0.262	−0.16	0.419	0.17	0.366	0.30	0.113
Phase angle (∘)	−0.10	0.346	−0.23	0.231	0.19	0.113	−0.23	0.239
Laboratory parameters								
Serum albumin (mg/dL)	0.01	0.936	−0.05	0.803	−0.01	0.950	−0.21	0.279
GFR (mL/min/1.73m^2)	0.24	**0.024**	0.07	0.726	0.11	0.564	−0.16	0.401
Glucose (mg/dL)	−0.03	0.759	0.23	0.213	−0.18	0.355	−0.09	0.634
Total-C (mg/dL)	0.30	**0.006**	−0.003	0.987	0.44	**0.018**	0.15	0.425
LDL-C (mg/dL)	0.30	**0.004**	0.02	0.906	0.46	**0.011**	0.45	**0.014**
HDL-C (mg/dL)	0.22	**0.040**	−0.11	0.548	0.23	0.224	−0.05	0.808
Non-HDL-C (mg/dL)	0.23	**0.029**	−0.002	0.993	0.22	0.249	0.36	0.058
LDL-C/HDL-C	0.16	0.143	0.15	0.422	0.19	0.338	0.40	**0.031**
Triglyceride (mg/dL)	0.11	0.320	−0.07	0.697	0.26	0.176	0.06	0.741
CRP (mg/dL)	−0.08	0.445	−0.05	0.805	0.01	0.967	−0.12	0.554
Ferritin (mg/dL)	−0.39	**<0.001**	−0.20	0.309	−0.24	0.210	−0.16	0.554
IL-6 (pg/mL)	0.20	0.076	0.52	**0.004**	0.004	0.982	0.17	0.407
Creatinine (mg/dL)	−0.26	**0.015**	−0.03	0.875	−0.10	0.616	0.20	0.308
TIBC (μg/dL)	0.22	**0.035**	−0.16	0.402	0.24	0.203	0.03	0.888
Atherogenic index	0.04	0.742	−0.02	0.902	0.12	0.542	0.21	0.270
REE (kcal)	−0.003	0.978	−0.25	0.187	0.18	0.355	0.21	0.273
Dietary intake								
Energy(kcal/kg/d)	−0.03	0.787	−0.26	0.162	0.11	0.571	0.08	0.671
Protein intake (g/kg/d)	−0.03	0.761	−0.14	0.459	0.02	0.924	0.17	0.368
MIS	−0.36	**<0.001**	0.05	0.809	−0.33	0.085	−0.23	0.231

Abbreviations: BMI – body mass index, C – cholesterol, WC – waist circumference, ECW – extracellular water, ICW – intracellular water, TBW – total body water, TIBC – total iron-binding capacity (µg/dL), FFMI – fat-free mass index, REE – resting energy expenditure, GFR – glomerular filtration rate, IL-6 – interleukin-6, MIS – malnutrition-inflammation score, CRP – C-reactive protein (mg/dL).

Table 4. Multiple linear regression for assessing association between adropin and related factors.

	Model 1			Model 2		
	β	S.E.	p value	β	S.E.	p value
MIS	−0.26	0.011	**0.031**	−0.25	0.001	**0.038**
LDL-C (mg/dL)	0.30	0.001	**0.003**	0.29	0.011	**0.007**
Ferritin (mg/dL)	−0.12	0	0.266	−0.12	0	0.291
GFR (mL/min/1.73m^2)	0.06	0.001	0.579	0.08	0.001	0.495

Notes: Model 1 – crude. Model 2 – adjusted for age + sex.
Abbreviations: MIS – malnutrition-inflammation score, LDL-C – low-density lipoprotein cholesterol, GFR – glomerular filtration rate, S.E. – standard error.

Similarly, Boric-Skaro *et al.* [5] reported that adropin levels were inversely correlated with body fat mass in hemodialysis patients. In addition, St-Onge *et al.* [30] demonstrated that plasma adropin concentrations correlated with fat consumption in women. The results of these studies suggest that adropin plays a role in energy homeostasis and protection against obesity. Further studies are needed to determine the association between adropin and obesity in patient with KFRT.

In patients with chronic KF, metabolic disorders contribute significantly to morbidity and mortality due to their close relationship with cardiovascular diseases. The search for new potential regulators of these abnormalities is important as they may be targets for the treatment of KF-associated pathology [37]. In the present study, patients with high adropin levels have been found to have higher LDL-C and total-C. Both univariate and multivariate analyses revealed a positive correlation between serum adropin

levels and LDL-C (Table 4). Contrary to these results, a recently published study found that adropin had a negative correlation with triglycerides, LDL-C, and total-C, and a significantly positive correlation with HDL-C in hemodialysis patients [5]. In a study conducted with adolescents, no relationship was found between HDL-C, triglyceride, total-C, and adropin levels [38]. In polycystic ovary syndrome patients, Yildirim *et al.* [39] showed that serum adropin levels were inversely correlated with serum lipid parameters (TG, TC, and LDL-C). Intraperitoneal administration of adropin decreased serum TG, TC, and LDL-C levels in hyperlipidemic rats [40]. In patients treated with HD, low plasma adropin concentration has been found to be associated with dyslipidemia [37]. Contrary to the studies mentioned above, the positive correlation between LDL and adropin levels in this study may be attributed to the fact that the patient's LDL-C levels were not very high compared to other studies.

Limitations

The present study had several limitations. First, it had a relatively small sample size. Second, this study was performed in a single-center, and these results should not be generalized to subjects of other races or nationalities. Third, causal relationships between adropin and malnutrition marker and lipid profile could not be concluded clearly from this study due to its cross-sectional design.

Conclusions

The current study demonstrated that adropin levels were higher in the transplantation group as compared to patients treated with hemodialysis and were similar in patients treated with hemodialysis and peritoneal dialysis. In patients with KFRT, serum adropin levels were found to be negatively correlated with malnutrition and positively correlated with lipid profile. These results might indicate that adropin somehow plays a role in the pathophysiological mechanisms and pathways and complications of patients with KFRT. However, studies with larger samples are needed to explain this relationship.

Ethical Statement

The study was approved by the Ethics Committee of Gazi University, Turkey (number: 35). Study procedures were performed according to the principles of the Declaration of Helsinki and written informed consent was obtained from all participants.

Informed Consent

Written informed consent was obtained from the patients in accordance with the Declaration of Helsinki.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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