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Original Article

Study of the Relationship between Serum Adropin Level and Nutritional Status in Hemodialysis Patients

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ABSTRACT

Background: Due to the high prevalence of cardiovascular risk factors, dyslipidemia, hyperinsulinemia, chronic low-grade inflammation, and malnutrition in chronic renal disease settings, an association with adropin can be reasonably hypothesized as it is a secretory protein encoded by the energy balance gene and is closely associated with regulation of energy metabolism and insulin resistance. This study aimed to evaluate possible associations between serum adropin level with nutritional status and other relevant laboratory parameters in hemodialysis (HD) patients.

Methods: The current case-control study was performed on eighty-eight subjects. We selected seventy-four HD patients and fourteen sex and age-matched healthy volunteers as a control group. Serum adropin level was analyzed among all participants with Subjective Global Assessment Score (SGAS).

Results: The mean adropin level in the patients' group was 2.62± 0.65 (ng/mL), and in the control group was 5.82± 0.73(ng/mL) with a high statistically significant difference ($p<0.001$). There was a significant positive correlation between HDL and adropin ($p=0.004$), but there was a negative significant correlation between cholesterol and adropin ($p=0.045$). The sensitivity of adropin in HD Patients was 56.67%, and the specificity was 83.33%, with an area under the curve of about 0.731 in cutoff point >2.4 to determine malnutrition. A significant positive correlation existed between malnutrition (mild, moderate, severe) and adropin. The significant predictors for serum adropin levels in HD patients were higher cholesterol levels, low-density lipoprotein (LDL), and higher body mass index (BMI) levels.

Conclusion: Adropin is potentially involved in the pathophysiological mechanisms of chronic kidney disease and HD patients and its complications like malnutrition.

Keywords: Adropin, chronic kidney disease, hemodialysis, malnutrition

INTRODUCTION

Hemodialysis (HD) is a mechanical method of detoxifying a patient with compromised renal function of their blood of excess fluid, minerals, and toxins. HD is a common renal replacement therapy, but it carries a substantial risk of cardiovascular complications, morbidity, and death for cases who had chronic kidney disease [1,2].

The energy homeostasis related (ENHO) gene encodes adropin, a new peptide that has been detected not only in the brain and liver but also in skeletal muscles, kidneys, pancreas, as well as the heart [3,4]. However, research has shown that adropin has a wide variety of actions, the most notable of which is

regulating glucose and lipid metabolism to keep energy levels stable [5-7].

Those with obesity and insulin resistance showed lower serum adropin levels, while those with a lower body mass index (BMI) had higher levels [8,9]. Increased research points to a possible involvement of adropin in the cardiovascular system. Multiple investigations suggested that adropin might be connected to vascular protection, neovascularization, and increased blood pressure.[10].

Additionally, Patients with coronary artery disease and low serum adropin levels have been shown to have an increased risk of developing an acute myocardial infarction, and serum adropin levels were shown to be significantly lower among cases who had coronary heart disease when compared to the healthy control group. Additionally, recent research is associating adropin with chronic inflammatory conditions, speculating that it may have an immunomodulatory impact [11].

Recent research has confirmed that HD patients had reduced serum adropin levels compared to healthy controls [12]. When comparing HD patients and healthy controls, however, other studies have shown no significant differences [13].

It is possible to determine the prevalence of malnutrition in HD patients using a fully quantitative scoring system called the SGA score-DMS. The SGAS-DMS is a helpful and valid index for nutritional assessment in HD patients, and it works effectively in tandem with anthropometric and biochemical testing to spot people at risk for malnutrition [14].

This work aimed to evaluate possible associations between serum adropin level with the status of the nutrition and other relevant laboratory parameters in HD patients.

METHODS

The current case-control study was performed on eighty-eight subjects; we selected seventy-four HD cases, and fourteen age and sex-matched healthy volunteers acted as a control group. This study was conducted in the HD unit and clinical pathology department at Zagazig University Hospitals from February 2022 to June 2023.

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Zagazig University (IRB#9285). The research was conducted in accordance with the Helsinki Declaration. A written informed consent was collected from the patients or their first-degree relatives.

Inclusion Criteria: cases aged between 18 and 65 years, experiencing HD and being stable for more than six months, with dialysis dose Kt/V from 1.1 to above 1.2, HbA1C < 7 %.

Exclusion Criteria: cases who had any of the following: history of stroke or uncontrolled Hypertension, Myocardial Infarction, autoimmune diseases, alcoholism, malignancies, liver diseases, receiving corticosteroids treatment, or had hypoglycemic episodes in the last three months before enrollment in the study.

All patients were subjected to:

Complete history taking including age, sex, duration of dialysis, dietary intake, daily activity, and GIT symptoms. Thorough clinical examination: Including vital signs and anthropometric measures. Laboratory investigations included complete blood count (CBC), Serum creatinine, Blood urea, C-reactive protein, HbA1C, lipid profile, total plasma protein, and albumin.

Special Investigations: Serum adropin level was analyzed by colorimetric assay for adropin using the Human adropin ELISA Kit. All procedures were conducted as described in the kit's manual. The enzyme-labeled device measured the absorbance at 450 nm to create the standard curve. The concentration of the sample was calculated using the standard curve. Values for optical density (OD) were within the range given by the manufacturer, and the coefficient variability (CV) of paired calibrations was less than 15%. The test had a linear range of 0.3 to 8.2 ng/mL, a sensitivity of 0.3 ng/mL, and a CV within the probe of less than 10%.

Modified Subjective Global Assessment Score (SGAS): consisting of seven variables, including dietary intake, weight change, gastrointestinal symptoms, functional capacity, comorbidity, signs of muscle wasting, and subcutaneous fat. Malnutrition score=sum of all numbers done according to the fully quantitative version of the SGA (Table 1): 7=normal or well nourished, 8-14=mild malnourished, 15-35 =moderate malnourished, and when >35 =severe malnourished [14].

Statistical Analysis

Data entered was analyzed using IBM's SPSS version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Descriptions in numbers and percentages were provided for the qualitative data as well. We compared qualitative variables using the Chi-Square (X2) test. Quantitative data was compared using the student's t-test. Regression analysis: used to rank the markers by how well they distinguish between the various patient groups. Analysis of variance (ANOVA) test was used in comparing three or more means (parametric quantitative data) for statistical significance. Pearson's correlation or Spearman's correlation was used to calculate the correlation between laboratory, anthropometric, and clinical parameters, and serum adropin levels. Additionally, multiple linear regression analysis of independent predictors for adropin levels was performed, with reporting the corresponding p values with unstandardized β-coefficients, standard error, and t-values.

RESULTS

This study enrolled seventy-four HD patients and fourteen healthy controls, and there were non-statistically significant differences between patients and controls regarding age and sex. (Table 2).

Triceps skinfold thickness, waist size, and body mass index measurements showed no statistically significant difference between the two groups (Table 3). In our study, the mean adropin in patients was 2.62± 0.65 (ng/mL), and in the control, it was 5.82± 0.73(ng/mL) significantly lower in the patient group compared to the control group ($p<0.001$).

There was a highly statistically significant relation between total SGA score and MUAC. There was a statistically significant relation between total SGAS and BMI, TSF, Albumin, cholesterol, and HDL (Table 4).

Mild malnutrition had statistically significant differences with Triceps skinfold (TSF), mid-upper arm circumference (MUAC), total proteins (T. Proteins), Albumin, cholesterol, HDL, total SGAS, and adropin (p=0.022, 0.012, 0.022, 0.025, 0.026, 0.016, 0.048, 0.041 respectively). Moderate malnutrition had statistically significant differences with TSF, MUAC, hemoglobin (Hb), T. Proteins, Albumin, cholesterol, HDL, total SGAS, and adropin (p=0.025, 0.025, 0.023, 0.031, 0.036, 0.017, 0.037, 0.035 respectively). Severe malnutrition had statistically significant differences with BMI, TSF, MUAC, Hb, T. Proteins, Albumin, cholesterol, HDL, total SGAS, and adropin (p=0.046, 0.018, 0.012, 0.011, 0.019, 0.039, 0.015, 0.002, 0.028 respectively) (Table 5).

Adropin was related significantly to cholesterol, HDL, and SGAS (p=0.045, 0.004, 0.028, respectively) (Table 6).

The sensitivity of adropin in HD patients was 56.67%, and the specificity was 83.33% under the curve of about 0.731 in cutoff point >2.4 to predict malnutrition in HD patients (Table 7, Figure S1).

In our study, the significant predictors for serum adropin levels in HD patients were higher cholesterol levels, HDL, and higher BMI levels (Table S1).

Table 1: The fully quantitative version of the SGA

(A) Patients related medical history				
1 - Weight change (overall change in past 6 months)				
1	**2**	**3**	**4**	**5**
No weight change	Minor weight loss (< 5%)	Weight loss 5-10 %	Weight loss 10-15%	Weight loss >15%
2 - Dietary intake				
1	**2**	**3**	**4**	**5**
No change	Sub-optimal diet	Full liquid diet or overall decrease	Hypo-caloric liquid	Starvation
3 – Gastrointestinal symptoms				
1	**2**	**3**	**4**	**5**
No symptoms	Nausea	Vomiting or moderate GIT symptoms	Diarrhea	Severe anorexia
4 – Functional capacity (nutritionally related functional impairments)				
1	**2**	**3**	**4**	**5**
None improved	Difficulty with ambulation	Difficulty with normal activity	Light activity	Bed/chair ridden
5 - Co-morbidity				
1	**2**	**3**	**4**	**5**
Dialysis < 12 month and normally co-morbidity	Dialysis 1–2yrs. or mild co-morbidity	Dialysis 2 – 4 yrs. or moderate co-morbidity or aged >75	Dialysis > 4 yrs. or severe co-morbidity	Very severe. co-morbidity
(B) Physical Exam				
1 - Decreased fat stores or loss of subcutaneous fat (eyes, Triceps, biceps, chest)				
1	**2**	**3**	**4**	**5**
None (no change)		Moderate		Severe
2 - Signs of muscle wasting (Temple, Clavicle, Ribs, knee, interosseous, quadriceps, scapula)				
1	**2**	**3**	**4**	**5**
None (no change)		Moderate		Severe
Malnutrition Score: (sum of all number)				

Table 2: Comparison between the cases and control groups according to demographic data

		Control group	**Patients group**	**T value**	**P-value**
		No. = 14	**No. =74**		
Sex	Female	9 (64.3%)	34 (45.9%)	2.400*	0.921
	Male	5(35.7%)	40 (54.1%)		
Age (years)	Mean ± SD	37.29± 3.30	41.54± 3.36	-1.898•	0.063
	Range	18 – 66	22– 60		

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

Table 3: Comparison between control group and patients' group regarding anthropometric measurements

		Control group No. = 14	Patients group No. =74	T value	P-value
TSF thick. (mm)	Mean ± SD	21.63± 2. 5	20.704± 1.9	2.583•	0.282
	Range	18 – 27	15 – 30		
MUAC (cm)	Mean ± SD	29.54 ± 0.16	28.06± 0.24	2.422•	0.257
	Range	26 – 36	24 – 33		
MAMC (cm)	Mean ± SD	22.74 ± 1.36	18.5±2.62	2.532•	0.063
	Range	16 – 26	15 – 23		
BMI (kg/m2)	Mean ± SD	23.15± 3.42	20.325± 1.92	1.722•	0.247
	Range	21 – 33	18.9 – 23.1		

MUAC: mid upper arm circumference, TSF: Triceps skinfold, BMI: body mass index, MAMC: mid-arm muscle circumference.
P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test; ≠: Mann-Whitney test

Table 4: Correlation between total SGAS and anthropometric measures

Variable	total SGAS	
	r	p
BMI	0.346	0.035*
TSF (mm)	-0.320	0.012*
MUAC (cm)	-0.405	0.001* *
HB (g/dl)	0.314	0.071
HbA1C (%)	0.341	0.060
CRP (mg/l)	0.017	0.450
T. Proteins (g/L)	-0.153	0.480
Albumin (g/L)	-0.476	0.047*
Urea (mg/dl)	-0.417	0.141
Creatinine (mg/dl)	0.246	0.862
Cholesterol mg/dl	-0.379	0.041*
HDL (mg/dl)	0.787	0.472
Triglycerides(mg/dl)	0.836	0.284

p: p value for comparing between the two studied groups χ^2: **Chi square test** MC: **Monte Carlo**
MUAC: mid upper arm circumference TSF: Triceps skinfold, HB: hemoglobin, BMI: body mass index, CRP: C reactive protein, HDL: High density lipoprotein

Table 5: Correlation between malnutrition and anthropometric measures

Variable	Mild malnutrition		Moderate malnutrition		Severe malnutrition	
	r	p	r	p	r	p
BMI	-0.146	0.514	-0.130	0.635	-0.130	0.046*
TSF (mm)	-0.178	0.022*	-0.316	0.025*	-0.356	0.018*
MUAC (cm)	-0.473	0.012*	-0.247	0.013*	-0.676	0.012*
Hb (g/dl)	0.654	0.371	0.378	0.023*	0.245	0.011*
HbA1C (%)	0.536	0.131	0.642	0.091	0.505	0.071
CRP (mg/l)	0.743	0.426	0.341	0.146	0.525	0.081
T. Proteins(g/L)	-0.380	0.022*	-0.369	0.031*	-0.581	0.019*
Albumin (g/L)	-0.318	0.025*	-0.379	0.036*	-0.376	0.039*
Urea (mg/dl)	0.853	0.164	0.426	0.742	0.356	0.725
Creatinine (mg/dl)	0.368	0.627	0.826	0.153	0.257	0.156
Cholesterol (mg/dl)	-0.728	0.026*	-0.526	0.017*	-0.617	0.015*
HDL (mg/dl)	0.579	0.016*	0.615	0.009*	0.731	0.002*
total SGAS	-0.656	0.048*	-0.627	0.037*	-0.517	0.025*
Adropin	-0.738	0.041*	-0.273	0.035*	-0.368	0.028*

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
MUAC: mid upper arm circumference TSF: Triceps skinfold, HB: hemoglobin, BMI: body mass index, CRP: C reactive protein, HDL: High density lipoprotein, SGAS: subjective global assessment score

Table 6: Correlation of adropin change with Laboratory, Anthropometric parameters

Variable	Adropin	
	r	P-value
Age (years)	0.333	0.072
Hb (g/dl)	-0.333	0.072
HbA1C (%)	-0.311	0.094
CRP (mg/l)	-0.080	0.675
T. Proteins (g/L)	-0.242	0.198
Albumin (g/L)	-0.274	0.175
Urea (mg/dl)	-0.405	0.061
Creatinine (mg/dl)	0.095	0.619
TSF thick. (mm)	-0.134	0.515
BMI (kg/m2)	-0.035	0.875
MUAC (cm)	-0.234	0.239
Cholesterol (mg/dl)	-0.389*	0.045*
HDL (mg/dl)	0.571**	0.004
SGAS	0.543*	0.028*

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
MUAC: mid upper arm circumference TSF: Triceps skinfold, HB: hemoglobin, BMI: body mass index, CRP: C reactive protein, HDL: High density lipoprotein, SGAS: subjective global assessment score

Table 7: Receiver operating characteristic curve (ROC) between patients' group and control group regarding adropin in HD Patients

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>2.4	0.731	56.67	83.33	77.3	65.8

DISCUSSION

Many studies have focused on the issue of malnutrition in the HD population. Various names, including protein-energy wasting and protein-energy malnutrition, often refer to malnutrition. Different degrees of inflammation, hypercatabolism, and elevated uremia contribute to malnutrition-inflammation-atherosclerosis and uremic wasting syndromes [15].

Adropin is a novel energy expenditure regulator affecting lipid and carbohydrate metabolism. Increased glucose uptake by skeletal muscles is thought to result from adropin's action on carbohydrate metabolism, which is mediated via the activation of pyruvate dehydrogenase. It improves glucose oxidation and insulin signaling in skeletal muscles [16]. Obesity, poor glucose metabolism, type 2 diabetes, and insulin resistance have all been linked to decreased adropin levels [9].

In our study, the mean age among the patient group was 41.54± 3.36 years, which was comparable with research done by Liman et al. [17] and Agboton et al. [18].

In our study, in the patient group, the mean BMI was 23.15± 3.42, and the mean MUAC was 28.06± 0.24. In a study on malnutrition screening by Roy et al. [19], 75% of patients were underweight; BMI, MAMC, and MUAC were16.6±3.09, 21.5±4.50, and 19.7±8.86, respectively. They concluded that protein-energy malnutrition, caused by inadequate calorie intake, was evident in HD patients based on the data from nutritional measures.

In our study, the mean adropin in patients was 2.62± 0.65 (ng/mL), and its average among control was 5.82± 0.73 (ng/mL), significantly lower in the patient group compared to the control group, which agrees with Boric-Skaro et al. [20] who stated that HD patients' serum adropin levels were substantially lower than those of the healthy controls. Contrary to our study, Kałużna et al. [12,13], in two studies in 2016 and 2019, revealed that serum adropin levels were not significantly different between dialysis patients and healthy control groups. Probable causes include the complexity of the role of adropin in different CVDs and patient populations, as indicated by contradictory data on adropin levels in cardiac dysfunction. The possibility of overlap between the study and other factors, such as coexisting disorders or other hormonal and metabolic factors, cannot be ruled out. It is not yet apparent how useful adropin is in diagnosing and predicting ESRD events in patients with cardiovascular illness.

Consistent with our findings, Grzegorzewska et al. [21] found that Higher adropin levels and decreased insulin resistance were discovered in individuals who were significant homozygotes for a particular polymorphism in the ENHO gene, and lower serum adropin levels were associated with HD group compared to controls.

In addition, Hu, and Chen [22] did another investigation on people with type 2 diabetes who had already acquired diabetic nephropathy and found that those patients' serum adropin levels were lower than expected.

According to the results presented above, adropin may play a role in the intricate pathophysiology of chronic kidney disease and HD. Lovren et al. [23], Aydin et al. [4], and other researchers have found that adropin helps control blood pressure and protect the blood vessels.

The oxidative stress pathway may also explain the link between adropin and HD. In a study on mice with generated nonalcoholic steatohepatitis, Chen et al. [24] found that deletion of adropin significantly exacerbated fibrosis and inflammation. Adropin, on the other hand, inhibited proinflammatory mediators and upregulated nuclear erythroid 2-related factor 2 (Nrf2), a significant regulator of cellular tolerance to oxidative stress, when given intraperitoneally.

Since oxidative stress is a characteristic of HD's pathophysiology due to toxin retention, nutritional deficiencies, antioxidant depletion

during dialysis, and low-grade inflammation, it is tempting to speculate that adropin's stimulation of Nrf2 reduces oxidative stress in HD cases [25].

Our findings revealed a significant negative correlation between the total SGAS and each of the TSF scores and MUAC, which was the same as mentioned in the study by Mahmoud et al. [26]. However, in the research performed by Espahbodi et al. [27], Patients' sex was significantly associated with their SGA score (P = 0.03), which may have resulted from the smaller female sample size.

Consistent with previous research on patients with chronic inflammatory diseases, Kuliczkowska-Paksej et al. [28] and Zang et al. [29] found that CRP and blood adropin levels have a weak inverse correlation that is not statistically significant. Researchers found that serum adropin levels were consistently lower in study participants than in healthy controls, raising the possibility that chronic inflammation was to blame.

Contrary to our study, Kałużna et al. [13] and Kałużna et al. [12] in their two studies, Patients on peritoneal dialysis were included, and there were much fewer men than women in the study population, both of which affected the outcomes.

Contrary to the findings of Yang et al. [30], who discovered that adropin levels decline with age, we found no statistically significant association between adropin and age.

Also, in the current study, a negative correlation was found between adropin and blood urea nitrogen but with a non-significant difference, which partially agrees with Kałużna et al. [13], who found inverse correlations between the level of adropin and BUN in the ESRD group.

In our study, a significant negative correlation was found between cholesterol and adropin and a positive significant correlation between HDL and adropin that coincides with the results in the study done by Boric-Skaro et al. [20], who stated that the correlation between HD participants' serum adropin concentrations and their lipid panel results. It was discovered that adropin correlates positively with HDL cholesterol and significantly negatively with triglycerides, low-density lipoprotein (LDL) cholesterol, and total cholesterol. Multiple other research has found a connection between lipid levels and adropin [3,7]

Furthermore, the hyper LDL cholesterolemic type of dyslipidemia was associated with a specific mutation of the ENHO gene, according to a study of HD patients with dyslipidemia; this mutation was also surprisingly associated with reduced cardiovascular mortality [21].

These results suggest that adropin is not necessary for dietary cholesterol uptake or cholesterol biosynthesis. However, increased cholesterol uptake through a feedback mechanism limits its creation in response to rising demand while regulating adropin expression. Research suggests that the consumption of particular macronutrients is the primary factor in adropin expression [7,31]

Childhood obesity has been linked to lower adropin levels [32]. In contrast, in patients with heart failure, one study has shown a positive connection between plasma adropin levels and body mass index [33]. An "obesity paradox" or "reverse epidemiology" has been described in people with end-stage renal disease. In a contradictory way, a greater body mass index is associated with improved outcomes [34].

In our study, there was a non-significant correlation between adropin and T. Proteins, Albumin, and BMI in the same way as the results in the study by Boric-Skaro et al. [20].

In our study, the significant predictors for serum adropin levels in HD patients were higher cholesterol level, HDL, and higher BMI levels and in agreement with Chang et al. [35] revealed that higher body fat percentages are correlated with lower adropin levels, implying that obesity may have a detrimental effect on adropin levels in the blood. Those patients were all obese, and all had some other condition—insulin resistance, diabetes, or metabolic syndrome that is known to suppress adropin expression.

Boric-Skaro et al. [20] revealed a substantial inverse association that was also discovered between adropin and the malnutrition inflammation score (MIS) and the dialysis malnutrition score (DMS), leading us to postulate that adropin is controlled by dietary intake. It is widely known that patients with HD often experience malnutrition due to

metabolic and hormonal abnormalities, insulin deficiency, insulin resistance, inflammation, insufficient dietary intake, and the negative consequences of renal replacement treatment [36].

The significant correlations between serum adropin level and nutritional status and other relevant laboratory indicators in HD patients are a remarkable contribution to the literature. This study's primary drawback is that it was performed on a tiny sample size at a single institution.

Conclusion

We conclude that adropin is potentially involved in the pathophysiological mechanisms of chronic kidney disease and HD patients and its complications like malnutrition.

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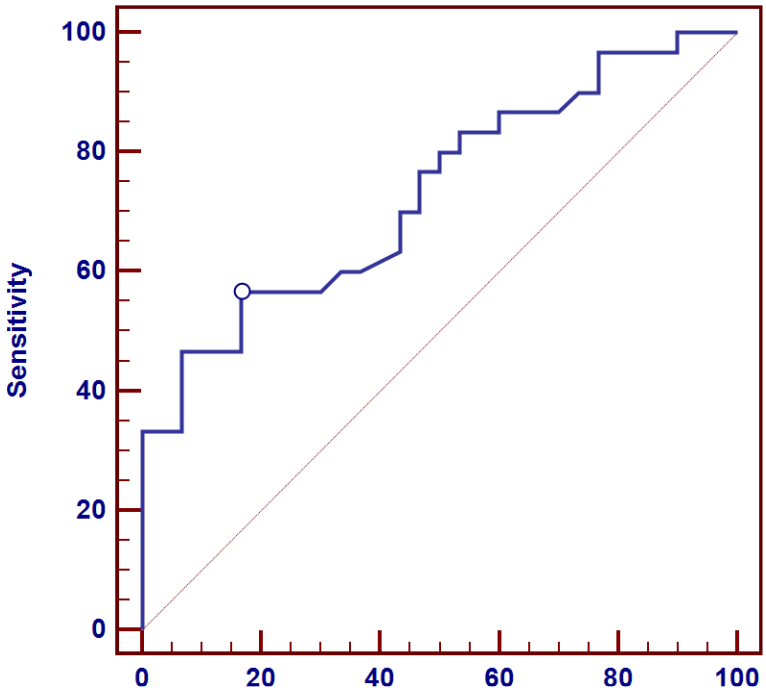

Figure S1: Receiver operating characteristic curve (ROC) between patients' group and control groupregarding adropin in hemodialysis patients

Table S1: Multiple linear regression model of independent predictors for serum adropin levels

Predictors	B	p-value	OR	95% CI	
				Lower limit	Upper limit
Cholesterol mg/dl	- 0.161	0.026*	0.851	0.739	0.981
HDL (mg/dl)	- 0.323	0.043*	0.724	0.529	0.990
Age	- 0.035	0.891	0.965	0.584	1.596
BMI	1.839	0.047*	6.290	0.944	41.895
CRP	0.019	0.067	1.019	0.999	1.041

B: Binary regression analysis OR: Odd ratio
HDL: high density lipoprotein, BMI: Body mass index, CRP: C reactive protein

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