

Adiponectin and ghrelin: nutritional regulatory role in chronic kidney disease patients

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Background

Adiponectin and ghrelin are orexigenic hormones involved in the regulation of appetite in kidney disease patients. The aim of the study is to investigate the plasma concentration of total adiponectin and ghrelin in hemodialysis (HD) patients, kidney transplant recipients (KTRs), and chronic kidney disease (CKD) patients not yet on regular dialysis.

Patients and methods

The study included 180 patients with a mean age of 34.6 ± 9.53 who were enrolled from the Nephrology Department of Cairo Medical School. Group 1 included 60 HD patients; group 2 included 60 KTRs. Group 3 included 60 participants with CKD not yet on dialysis. Anthropometric measures of all patients were taken. All participants were investigated for adiponectin, ghrelin, lipid profile, albumin, and hemoglobin. Adiponectin and ghrelin were correlated with variable parameters.

Results

One hundred and eight patients (60%) were men. Adiponectin was significantly higher in HD patients than KTRs and CKD groups (17 ± 3.5 , 10.8 ± 5.2 , and 4.7 ± 2.3 , respectively). Ghrelin was lower in KTRs compared with HD and CKD groups (2.1 ± 0.2 , 2.8 ± 0.25 , 2.8 ± 0.3 , respectively, $P < 0.001$). Adiponectin and ghrelin were inversely correlated with BMI in all studied groups.

Conclusion

Adiponectin and ghrelin levels were highest in HD patients. Adiponectin was superior to ghrelin as a positive predictor of nutritional status in CKD.

Keywords:

adiponectin, chronic kidney disease, ghrelin, lipid profile, nutritional status

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Introduction

End-stage kidney disease (ESKD) is a chronic condition associated with malnutrition, whether obesity or undernutrition. These factors contribute to an increase in both morbidity and mortality, especially in hemodialysis (HD) patients [1].

Different mechanisms are accused of being responsible for protein–energy wasting in ESKD, including inflammatory status, comorbidities, and anorexia. Orexigenic or appetite stimulants (ghrelin and adiponectin) and anorexigenic or appetite suppressants (leptin and cholestatin) are involved in regulating the appetite [2]. The secretion of such hormones is influenced by the interplay of the central hypothalamic signals and the metabolic status of the peripheral tissues [3].

The levels of adiponectin, ghrelin, and other anorexigenic hormones in renal dysfunction is quite variable and such variability has a strong influence on their classic feedback [4,5].

Adiponectin is exclusively secreted from adipose tissue into the blood stream. Its levels are inversely correlated

with the body fat percentage [6]. It plays a role in the suppression of metabolic derangements of type 2 diabetes and is an independent risk factor for metabolic syndrome in high-risk cardiovascular disease patients [7]. High adiponectin levels are associated with a higher mortality risk in HD patients [8].

Ghrelin remains the only known peripherally produced and centrally acting orexigenic hormone [9]. Although secreted into the blood stream primarily from endocrine cells within the stomach, evidence suggests that other tissues may also synthesize ghrelin, including the kidney [10]. Ghrelin is metabolized and secreted by the kidneys in normal individuals [11]. It may play an important role in the pathogenesis of protein–energy wasting, inflammation, and cardiovascular complications in chronic kidney disease (CKD) [12].

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Although there are many studies addressing the nutritional status of ESKD patients [13–15], in Egypt, there are no available literature studying the correlation between the nutritional status of ESKD patients and kidney transplant recipients (KTRs) and different appetite-regulating hormones notably ghrelin and adiponectin. The current study aims to assess the level of both ghrelin and adiponectin in HD patients, KTRs, and CKD not on HD.

Patients and methods

This is an observational cross-sectional study conducted on 180 participants who were enrolled consecutively from the Nephrology Department, who were divided into three groups:

Group 1 included 60 HD patients receiving three sessions per week, each lasting for 4 h for more than 5 years and less than 10 years.

Group 2 included 60 KTRs with a serum creatinine (SCr) less than 1.5 mg/dl and having received a graft more than 2 years ago.

Group 3 included 60 CKD patients not on HD.

Patients less than 18 years, those with diabetes mellitus, autoimmune disease, infection, decompensated liver disease, any current acute illness in the previous 3 months prior to the study, or those with positive family history of dyslipidemia were excluded from this study. Patients on any antibiotics, multivitamin, or food supplements apart from folic acid or vitamin B were also excluded.

All participants were subjected to full history taking and clinical examination. All patients had their nutritional status assessed both clinically and by laboratory. Anthropometric measures included weight, height, and BMI. The participants were classified as normal weight, if their BMI was between 18.5 and 25 kg/m², overweight if their BMI was more than 25.0 kg/m², and underweight if their BMI was less than 18.5 kg/m². Triceps skin fold (TSF) was also assessed. Patients stood with relaxed shoulders and freely hanging arms. After placing the jaws of the calipers at the level of marked midpoint of the upper arm circumference while grasping the fold of the skin and subcutaneous adipose tissue gently with thumb and forefingers, ~1.0 cm above the marked points, we recorded the measured skin fold thickness to the nearest 1 mm. If two measurements were within 4 mm of each other, the mean was recorded. If the measurements were more than 4 mm apart, four measurements were recorded and the mean was recorded.

Nutritional status was assessed in the laboratory by measuring both serum adiponectin and ghrelin. Serum adiponectin was measured by Orgenium Laboratories' human adiponectin enzyme-linked immunosorbent assay test that is a solid-phase enzyme-linked immunosorbent assay designed to measure the quantitative amount of total (low, middle, and high molecular weight) human adiponectin. The procedure includes standard samples, biotinylated antihuman adiponectin pipetted into the wells, and adiponectin present in a sample was captured by the antibody immobilized to the wells, and by the biotinylated adiponectin-specific detection antibody. Serum ghrelin was measured by a double-antibody sandwich technique. The wells of the plate supplied with the kit were coated with a monoclonal antibody specific to the C-terminal part of ghrelin. The concentration of human acylated ghrelin was then determined by measuring the enzymatic activity of immobilized AChE using Ellman's reagent. Serum urea, SCr, fasting blood sugar (FBS), albumin, hemoglobin (Hb), cholesterol, and triglycerides were estimated using the automated method (colometric technique).

The Modification of Diet in Renal Disease (MDRD) equation was used to calculate the glomerular filtration rate (GFR) as follows: estimated glomerular filtration rate (eGFR) (ml/min/1.73 m²) = $186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if woman}) \times (1.210 \text{ if Afro American})$ [16]. The aforementioned laboratory parameters were measured in HD patients before a long dialysis-free weekend interval before the next HD session, as recommended.

The study protocol conformed to the ethical guidelines of 1975 of the Helsinki Declaration and was approved by the Ethics Committee of Internal Medicine, Faculty of Medicine, Cairo University. Written informed consents were obtained from the participants in this study.

Data were analyzed using the statistical package SPSS, version 12 ((Hong Kong) Ltd, Rm 1804, 18/F, Westlands Centre, Westlands Road, Quarry Bay, Hong Kong). Number and percent were used to summarize qualitative variables. Mean and SDs were used to summarize quantitative variables. One-way analysis of variance test was used to compare more than two groups as regards the quantitative variables. *P* value less than or equal to 0.05 was considered statistically significant. Tables and graphs were used to illustrate information.

Results

Mean patients' age was 34.6 ± 9.53 years. Sixty percent (108 patients) were men, while 40% (72) were women. Most patients (126/70%) were eutrophic, 30 (16.7%) were overweight, and a BMI less than 18.5% was noticed in 24 (13.3%).

No statistically significant difference was noted between the studied groups, regarding age, sex, anthropometric parameters, duration of disease, and FBS. There was a highly significant difference between the studied groups regarding Hb level, serum urea and SCr, albumin, total cholesterol and triglycerides, adiponectin and ghrelin levels. Adiponectin levels were significantly higher in HD patients and KTRs compared with CKD patients (17.3 ± 3.5 and 10.8 ± 5.2 vs. 4.7 ± 2.3), respectively with an F value of 82. Ghrelin was significantly lower in KTRs, than in both HD and CKD patients (F value=15, $P \leq 0.001$). Demographic, anthropometric, and laboratory parameters among the studied groups are summarized in Table 1.

When correlating adiponectin and ghrelin levels to various variables, they were found to be inversely correlated to BMI in all groups with a significant value. Ghrelin was negatively related to eGFR and

accordingly positively correlated with SCr in both HD and CKD groups ($r = -1.3$ and $r = 0.9$), respectively, with P value less than 0.001. The correlation of both ghrelin and adiponectin with different variables is illustrated in Table 2.

There was no significant difference between women and men regarding the level of adiponectin and ghrelin among the studied groups.

Adiponectin had a higher sensitivity than ghrelin in detecting the nutritional status of the patients in HD, CKD patients, and KTRs. The performance of adiponectin and ghrelin as markers of BMI in the different groups is depicted in Table 3.

Discussion

The current study found a significant difference between the nutritional status of HD patients, compared with KTRs and CKD patients and this is in accordance with McCollum *et al.* [17], who showed that there is a high prevalence of protein-energy malnutrition in HD patients; however, the present study showed no significant difference regarding BMI among the participants.

Table 1 Demographic, anthropometric, and laboratory characteristics of the studied participants

Variables	Group 1	Group 2 (renal transplant (N=60) (mean±SD)	Group 3 (chronic kidney disease) (N=60) (mean±SD)	P value	Post-hoc test (LSD)
Age (years)	38±11.6	34±9	32.9±8	>0.05 (NS)	
Duration of the disease (years)	4.9±3.2	3.3±3	3.2±2.6	>0.05 (NS)	
Sex [n (%)]				>0.05 (NS)	
Male	32 (53.3)	42 (70)	34 (56.7)		
Female	28 (46.7)	18 (30)	26 (43.3)		
Weight (kg)	63±12	60±14	65.9±7	>0.05 (NS)	
Height (cm)	160±7.7	162±13	168±11	>0.05 (NS)	
SFT (mm)	6.9±1.7	7.9±3	6.8±3.3	>0.05 (NS)	
BMI					
Mean±SD	22.9±2.2	23±4.5	23.5±3.4	>0.05 (NS)	
<18.5	2 (3.33)	8 (13.33)	40 (66.7)	<0.001 (HS)	
18.5–24.9	46 (76.6)	40 (66.66)	14 (23.3)	>0.05 (NS)	
≥25	12 (20)	12 (20)	6 (10)	>0.05 (NS)	
eGFR	16.9±4	79.8±16	44.2±16.6	<0.001 (HS)	2 vs. 1 and 3
Hemoglobin (g/dl)	9.9±2.2	12.4±1.1	9.3±0.7	<0.001 (HS)	2 vs. 1 and 3
Creatinine (mg/dl)	9.3±2.3	1.1±0.19	3.09±0.8	<0.001 (HS)	1 vs. 2 and 3 3 vs. 2
Urea (mg/dl)	137±30	35±13	98.4±5.5	<0.001 (HS)	1 vs. 2 and 3 3 vs. 2
Triglyceride (mg/dl)	123.7±50	184.7±81	94±18	<0.001 (HS)	2 vs. 1 and 3 1 vs. 3
Cholesterol (mg/dl)	135.6±35	200.7±70	129.7±36	<0.001 (HS)	2 vs. 1 and 3 1 vs. 3
Albumin (g/dl)	3.7±0.4	4.4±0.6	3.4±0.3	<0.001 (HS)	2 vs. 1 and 3 1 vs. 3
Fasting blood sugar (mg/dl)	77.6±10	78.7±10	79.3±7	>0.05 (NS)	
Serum adiponectin (µg/ml)	17±3.5	10.8±5.2	4.7±2.3	<0.001 (HS)	1 vs. 2 and 3 2 vs. 3
Ghrelin (µg/ml)	2.8±0.25	2.1±0.2	2.8±0.3	<0.001 (HS)	2 vs. 1 and 3

eGFR, estimated glomerular filtration rate; HS, highly significant; LSD, least significant difference; SFT, skin fold thickness.

Table 2 Correlation of adiponectin and ghrelin versus general data among the studied groups

Variables	Group 1 (hemodialysis)		Group 2 (renal transplantation)		Group 3 (chronic kidney disease)	
	Ghrelin	Adiponectin	Ghrelin	Adiponectin	Ghrelin	Adiponectin
Age (years)						
R value	-0.23	-0.04	-0.21	0.14	-0.20	-0.11
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Duration (years)						
R value	0.07	0.06	0.03	0.1	0.06	0.09
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
BMI%						
R value	-0.09	-0.33	-0.39	-0.41	-0.32	-0.28
P value	>0.05	<0.05 (S)	<0.05 (S)	<0.05 (S)	<0.05(S)	<0.05 (S)
Hb %(g/dl)						
R value	-0.12	0.09	-0.22	-0.01	-0.42	-0.011
P value	>0.05	>0.05	>0.05	>0.05	<0.05 (S)	>0.05
eGFR						
R value	-0.35	-0.1	-0.13	-0.1	-0.33	-0.09
P value	<0.05 (S)	>0.05	>0.05	>0.05	<0.05 (S)	>0.05
Creatinine (mg/dl)						
R value	0.32	0.02	0.12	0.13	0.34	0.10
P value	<0.05 (S)	>0.05	>0.05	>0.05	<0.05 (S)	>0.05
Triglycerides (mg/dl)						
R value	-0.03	-0.22	-0.17	-0.20	-0.12	-0.13
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Cholesterol (mg/dl)						
R value	-0.14	-0.18	-0.13	-0.19	-0.11	0.10
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
FBS (mg/dl)						
R value	0.07	0.21	-0.10	0.20	-0.45	0.10
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Albumin (mg/dl)						
R value	0.02	-0.26	0.04	-0.14	0.09	-0.16
P value	>0.05	<0.05 (S)	>0.05	>0.05	>0.05	>0.05
SFT (mm)						
R value	0.29	0.19	0.19	0.32	0.18	0.12
P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; Hb, hemoglobin; S, significant; SFT, skin fold thickness. Bold values significant statistical results only.

Table 3 Receiver operating characteristic curve analyses of ghrelin and adiponectin in prediction of nutritional status (abnormal BMI)^a among different study group

Variables	All studied case		Group 1 (hemodialysis)		Group 2 (renal transplantation)		Group 3 (chronic kidney disease)	
	Adiponectin	Ghrelin	Adiponectin	Ghrelin	Adiponectin	Ghrelin	Adiponectin	Ghrelin
Best cut off	11.25	2.31	8.4	2.15	8.4	2.15	8.5	2.1
Area under the curve	0.709	0.701	0.769	0.606	0.769	0.606	0.701	0.75
Sensitivity (%)	74.3	66.4	73.3	66.7	73.3	66.7	77	62
Specificity (%)	73.3	73.3	66.7	66.7	66.7	66.7	65.6	50
PPV (%)	73.3	73.3	66	66	66.7	66.7	68	55
NPV (%)	73.3	64.7	72	64	70.8	66.7	72	65

NPV, negative predictive value; PPV, positive predictive value. ^aAbnormal BMI means beyond the normal reference range.

Anja *et al.* [18] and Ocak *et al.* [19] stated that BMI is significantly higher in KTRs, compared with CKD patients and HD patients. The absence of such a difference in our study may be explained by the small sample size and different ethnicity of the studied populations.

Levels of cholesterol and triglycerides, as well as serum albumin and Hb were all significantly higher in KTRs, compared with HD or CKD patients, respectively. Only FBS showed no significant difference among the studied groups. Dyslipidemia in KTRs is a consistent finding in most KTRs studies [20,21]. The variation in lipid

pattern in such patients appears to be multifactorial, influenced mainly by the use of immunosuppressive drugs, namely cyclosporine [22].

Adiponectin and ghrelin are hormones the secretion of which is affected by various factors such as fasting, age, and mainly the BMI normal range of adiponectin in the lean population is 4–37 $\mu\text{g/ml}$ while that of ghrelin is 520–700 pg/ml . Prior studies stated that both adiponectin and ghrelin levels are elevated in CKD and HD patients [23,24]. This may be attributed to the inflammatory and poor nutritional status of these patients [23]. Reduced GFR may also lead to elevated ghrelin levels. This was found to be in agreement with the current study that showed that the adiponectin level in HD patients was higher than in KTR and CKD patients (17 vs. 10.8 and 4.7, respectively). Similarly, Ocak *et al.* [19] also demonstrated a higher adiponectin level in HD patients compared with KTR and CKD patients.

Chudek *et al.* [23] found that before renal transplantation, adiponectin was significantly higher than in healthy participants and that after successful KT, adiponectin level significantly decreased ($P < 0.001$). Unlike our results, Leibowitz *et al.* [25] had found that KTRs had adiponectin levels similar to adiponectin levels in normal controls. Adiponectin may have protective effects on the kidney, although higher levels have not been associated with better graft survival in KTRs [26].

Ghrelin levels were higher in the HD and CKD groups (2.8 ± 0.25 and 2.8 ± 0.3 , respectively) compared with KTRs (2.1 ± 0.2). This was in agreement with many previous studies [19,27]. A previous study showed furthermore that HD patients with failed renal transplants had higher ghrelin levels, higher inflammation, poorer appetite, with malnutrition as compared with HD patients who had never been transplanted suggesting that ghrelin may be associated with inflammation caused by retained failed allografts [28].

Contrarily, Iglesias *et al.* [29] found that adult HD patients had significantly lower serum ghrelin concentrations, than predialysis CKD patients.

When correlating adiponectin to BMI, the current study demonstrated a significant inverse correlation between them in all groups, which is consistent with other studies that found that plasma adiponectin levels were strongly and inversely related to BMI in CKD and HD. Ghrelin was also negatively correlated with BMI in the studied population with statistically significant

values in HD, KTRs, and CKD patients [23,30]. This is somewhat going with the previous studies showing an inverse correlation between ghrelin and BMI in CKD and HD patients [31,32]. Genis *et al.* [33] also found a significant negative correlation between ghrelin and both BMI and GFR in KTRs in previous studies. Our results also showed that ghrelin was inversely correlated to eGFR and positively correlated to SCr in both HD and CKD groups with a significant value.

A recent study in children showed that unacylated ghrelin and obestatin are negatively related to renal function and are inverse indicators of the nutritional status in children with CKD hypothesizing the potential therapeutic implications in terms of optimization of their removal in HD patients [34]. The elevation of ghrelin levels could be caused by impaired renal clearance and/or metabolism of ghrelin [35]. Alternatively, adiponectin was not correlated to eGFR, giving it the advantage of being an independent marker of nutrition in renal diseases population. Our results are contradictory to many prior studies that reported a negative correlation between adiponectin and eGFR [36,37].

The study has shown that there was no relation between both adiponectin and ghrelin levels versus fat mass measured by the TSF, despite its relation to BMI. This is contrary to a previous study that concluded that adiponectin was negatively correlated with TSF [4]. This can be for the fact that TSF does not reflect the whole body fat composition and distribution. An additional rationale is that in the present study we did not include proportionate numbers of obese patients ($\text{BMI} > 25$). Moreover, adiponectin secretion depends on visceral fat rather than subcutaneous fat [38]. The present study noticed that neither adiponectin nor ghrelin was affected by sex, age, or duration of the disease among all studied groups. This is not in accordance with previous studies that precluded that age, sex, renal disease duration, and visceral fat were independently associated with adiponectin levels in CKD patients [39]. Moreover, various studies demonstrated that plasma adiponectin levels and ghrelin were higher in uremic women than men and that this difference remained significant even after adjustment for BMI [40]. This was also observed in healthy control participants [24].

Among the study groups, there was no correlation between ghrelin and other laboratory nutritional parameters including lipid profile, Hb, and FBS. This coincides with previous studies showing that

Hb, triglycerides, albumin, and cholesterol were not related to ghrelin levels [31,33]. Adiponectin also exhibits the same findings. This is in contrast to the published work by Zoccali *et al.* [24] and Menon *et al.* [41], who detected a significant correlation between adiponectin and both lipid profile and blood sugar.

Adiponectin was negatively related to albumin in HD patients only. This may be explained by the fact that adiponectin is a multifunctional cytokine which has a role in regulating inflammation [5]. It may be related to albumin synthesis, albumin being a negative phase reactant agent [40].

In an attempt to compare the value of adiponectin and ghrelin and assessing their relation to the nutritional status in various renal dysfunction groups, it was observed that adiponectin has a higher sensitivity than ghrelin in HD and KTR groups; thus, it is a better positive predictor than a negative predictor of abnormal BMI and nutritional status.

Limitations of the study include the small-sized sample, lack of long-term follow-up to detect morbidity and mortality outcomes and to trace correlation between adiponectin and ghrelin levels and nutritional consequences and finally the lack of complementary investigations of body composition and measurements for more precise informative results. The study addresses the effect of both hormones among renal patients in the same sitting which could be determinant of the nutritional state in such patients for early recognition and predicting patients' outcomes.

Conclusion

Our study has shown that both adiponectin and ghrelin were negatively correlated to BMI in HD patients and KTRs and that adiponectin was superior to ghrelin, as a surrogate marker of the nutritional state in this population of patients.

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Conflicts of interest

There are no conflicts of interest.

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