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# Determining the alteration of ghrelin and some biochemical parameters in end-stage kidney disease patients on hemodialysis

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**ABSTRACT**

**Introduction:** Renal failure is a pathological condition characterized by impaired renal excretion of end-products of metabolism.

**Objectives:** The present study aimed to assess ghrelin hormone and certain biochemical parameters such as urea, creatinine, uric acid, albumin, total protein, alkaline phosphatase (ALP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c) and very low-density lipoprotein (VLDL) in the serum of hemodialysis patients compared with healthy subjects.

**Patients and Methods:** In this cross-sectional study, a total of sixty end-stage kidney disease patients on hemodialysis were enrolled from Ibn Sina dialysis center in Baquba teaching hospital, Iraq (May 2022 to October 2022). Moreover, thirty healthy volunteers served as control subjects in this study.

**Results:** The results indicated a significant decrease in serum ghrelin levels of hemodialysis patients compared to the controls ($P<0.05$). Notably, patients exhibited elevated levels of serum urea, uric acid and creatinine in comparison to the controls ($P<0.05$). Moreover, serum albumin level was found to be decreased in patients as compared to controls too ($P<0.05$). However, the levels of total protein did not exhibit any significant differences between the groups ($P>0.05$). A significant negative association between serum ghrelin and urea was detected ($P<0.05$).

**Conclusion:** The level of ghrelin was found to be significantly reduced in patients with renal failure. Therefore, the decreased levels of ghrelin may serve as a potential predictor of kidney insufficiency in patients with chronic kidney disease.

*Implication for health policy/practice/research/medical education:*
In a study on 60 end-stage kidney disease patients on hemodialysis we found a relationship between renal failure and Serum ghrelin concentration. It seems that decreased ghrelin levels linked with kidney failure, and can be conducted as independent biomarker in diagnosis of kidney disease.

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## Introduction

Renal insufficiency is connected to the incapability of the kidneys to perform excretory functions which results in the retention of nitrogenous byproducts in the plasma. Renal insufficiency pertains two distinct categories as acute kidney injury and chronic kidney disease (CKD) (1). Acute kidney injury is distinguished by a sharp collapse of kidney function, as evaluated by elevated levels of creatinine in the blood and decreasing urine output (oliguria), and is limited to a duration of one week (2). This condition is a sign of a vast range of functional renal disorders conjointly known as acute kidney disease, which varies in severity from mild and self-limiting to severe and chronic (3). Chronic kidney disease described as renal damage or an estimated glomerular filtration rate of less than 60 mL/min per 1.73 $m^2$ that persists for a period beyond three months. It is a condition indicated by the continuous degeneration of kidney function, essentially demanding the use of renal replacement therapy (dialysis or transplantation) (4). Ghrelin is a peptide hormone produced in the stomach. Ghrelin released in the bloodstream during a state of negative energy balance as the hunger hormone (5). The main producers of this 28-amino-acid hormone

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are the cells of the oxyntic gland in the gastric mucosa. Ghrelin expression has also been observed in the kidneys, pancreas, heart, lungs, and placenta, among other organs (6). The growth hormone secretagogue receptor, also known as the ghrelin receptor, plays a role in the biological activities of ghrelin. Finding the positive effect of ghrelin on food intake and meal enjoyment, make it as a potential to serve as a beneficial treatment option for anorexic CKD patients (7). Orexigenic hormones, such as adiponectin and ghrelin, are implicated in the regulation of appetite in individuals with renal disease (8,9). Administration of exogenous gut ghrelin has shown to excise a protective effect on the kidneys through anti-oxidative mechanisms (9). The antioxidative impact of ghrelin can be credited to its antagonistic effect on plasma renin activity and angiotensin II receptor type 1. Previous studies showed the effects ghrelin were observed through the reduction of plasma renin activity levels and downregulation of angiotensin II receptor type 1 expression (10). Generally, adiponectin surpassing ghrelin as a superior predictor of nutritional status in CKD (8,10,11).

## Objectives

The aim of this study was to investigate the relationship between CKD-associated renal insufficiency and alterations in ghrelin hormone levels.

## Patients and Methods

### *Samples collection*

In this cross-sectional study, collection of samples was conducted from May 2022 to December 2022. A total of 60 blood samples were obtained from hemodialysis patients at Ibn Sina dialysis center in Baqubah teaching hospital, located in Baqubah city within the Diyala governorate. Among the samples, there were thirty-eight male patients and twenty-two females. The age range of patients were from 20 to 75 years. Additionally, thirty blood samples were collected from apparently healthy individuals to serve as a control group. The control group consisted of sixteen male subjects and fourteen female subjects, with the age range of 20 to 75 years. Each collected blood sample was then placed in a gel tube and allowed to clot. Serum separation from samples was conducted using a centrifuge device, which worked for five minutes at a speed of 3000 cycles per minute. The retained serum from each sample was divided into two. The first part of the serum, consisting of 200 µL, was placed in a small tube and stored at a temperature of -20 °C until it was used for the estimation of ghrelin. The second part of the serum was conducted for other measurements for example; urea, creatinine, uric acid and albumin. Body mass index (BMI) calculation required dividing weight in kilograms by height in meters ($kg/m^2$) (12).

### *Clinical analysis*

Serum ghrelin was measured by the enzyme-linked immunosorbent essay (ELISA) kit (Shanghai Co. China). The analysis of fasting serum lipid profile (triglyceride [TG], total cholesterol [TC], and high-density lipoprotein cholesterol [HDL-c]), urea, creatinine, and uric acid was conducted using an automated chemical analyzer (COBSe 411, Germany). Accordingly, total protein, albumin, and alkaline phosphatase (ALP) was measured commercially available laboratory kits (Mindray Company; China). The calculation of low-density lipoprotein (LDL-c) was conducted using the equation; LDL=[cholesterol]-[HDL]-{[TG]/5}. Additionally, the calculation of very low-density lipoprotein (VLDL) was conducted using the formula; VLDL = [TG]/5 (13,14).

### *Statistical analysis*

Statistical analysis was conducted using the SPSS software (version 25) to examine the statistical variables. The results were reported as mean ± standard deviation (Mean ± SD). For correlations Pearson's correlation test was conducted. The significance of the differences between the traditional statistical variables was further assessed using chi-square test and *t* test. The selected significance level was set at $P<0.05$.

## Results

### *Anthropometries assessments*

In terms of gender, the patient group consisted of 63.3% males and 36.7% females, whereas the healthy control group comprised 52.5% males and 47.5% females. In this study no statistically significant difference between females in the patients group and those in the healthy group was seen ($P>0.05$). However, there was a significant difference between males in the patients group and those in the healthy control group ($P<0.05$).

This study indicated significant differences in age distribution between patients and healthy individuals ($P<0.05$). The age group of 41-60 years had the highest percentage among patients (51.7%), while the age group of 21-40 years had the highest percentage among healthy individuals (80.0%). The age group over 60 years had the lowest percentage of patients (20.0%) and healthy individuals (5.0%).

There were no significant differences ($P>0.05$) in BMI levels between patients and healthy individuals, except for the underweight BMI category, which had a higher percentage among patients (41.7%) compared to the healthy individuals (25.0%), with statistically significant differences ($P<0.05$; Table 1).

### *Renal function parameters*

To the study findings presented in Table 2 demonstrate that the levels of serum urea, uric acid and creatinine in patients were elevated with exhibiting a significant disparity ($P<0.05$). The serum albumin was owner in patients with a significant difference ($P<0.05$) compared to the healthy control group. In terms of total protein, the

observed outcomes indicate a lack of significant differences between the groups under investigation ($P<0.05$).

### *Lipid profile in studied groups*

The findings from Table 3 displayed modifications in the lipid profile of individuals suffering from kidney failure in comparison to those who are deemed healthy. A significant decrease in the level of HDL-c was observed among patients when compared to the healthy controls ($P<0.05$). Conversely, there was a significant increase in the levels of cholesterol and VLDL-c among patients as opposed to the healthy controls ($P<0.05$). Our results did not exhibit any significant differences in the LDL-c and TG parameters between the groups ($P>0.05$).

### *ALP and ghrelin in studied groups*

The ALP parameter exhibited an increase in patients in comparison to the healthy controls with a remarkably significant disparity ($P<0.001$). Similarly, serum ghrelin level decreased in patients ($0.23\pm0.73$ ng/mL) when contrasted with the healthy controls ($0.80\pm0.46$ ng/ml), also with revealing a highly significant difference ($P<0.001$) as depicted in Table 4.

### *Relationships among variables*

The outcomes of the present investigation have revealed that serum ghrelin exhibits a non-significant and positive relationship with HDL-c ($r=0.111$), albumin ($r=0.143$), and protein ($r=0.117$). Conversely, serum ghrelin displays a non-significant and negative association with serum creatinine ($r=-0.129$), cholesterol ($r=-0.167$), LDL-c ($r=-0.153$), TG ($r=-0.242$), ALP ($r=-0.108$), and VLDL-c ($r=-0.242$) as showed in Table 5. Finally, it is noteworthy that serum ghrelin exhibits a significant and negative correlation with urea ($r=-0.256$) as depicted in Figure 1.

## Discussion

The present investigation demonstrated notable disparities between patients with renal failure and healthy individuals with regard to gender, and these findings are in accordance with the results of the study conducted by Hödlmoser et al (11). Gender disparities play a pivotal role in the majority of diseases. However, the implementation of a gender-specific approach to the prevention and treatment of CKD, as well as the adherence to clinical practice guidelines and research, has largely been disregarded (15). In the United States, women exhibit less awareness about CKD compared to men. Furthermore, women have a higher incidence of CKD than men, although they are less likely to progress to end-stage kidney disease, as indicated by several epidemiological studies (16). The findings indicate an increase in CKD with advancing age. According to a

**Table 1.** Baseline characters of participants are calculated by chi-square test

| | | | Groups | | Total | *P* value |
|---|---|---|---|---|---|---|
| | | | Patients | Healthy | | |
| Gender | Males | N | 38 | 21 | 59 | <0.05 |
| | | % | 63.3 | 52.5 | 59.0 | |
| | Females | N | 22 | 19 | 41 | >0.05 |
| | | % | 36.7 | 47.5 | 41.0 | |
| *P* value | | | <0.05 | >0.05 | >0.05 | |
| Age groups (years) | 21-40 | N | 17 | 32 | 49 | <0.05 |
| | | % | 28.3 | 80.0 | 49.0 | |
| | 41-60 | N | 31 | 6 | 37 | <0.001 |
| | | % | 51.7 | 15.0 | 37.0 | |
| | >60 | N | 12 | 2 | 14 | <0.01 |
| | | % | 20.0 | 5 | 14.0 | |
| Mean±SD | | | 48.65±13.32 | 33.65±10.92 | 40.33±18.21 | <0.001 |
| BMI groups (kg/m²) | Underweight | N | 25 | 10 | 35 | <0.05 |
| | | % | 41.7 | 25.0 | 35.0 | |
| | Normal weight | N | 17 | 13 | 30 | >0.05 |
| | | % | 28.3 | 32.5 | 30.0 | |
| | Overweight | N | 11 | 10 | 21 | >0.05 |
| | | % | 18.3 | 25.0 | 21.0 | |
| | Obesity | N | 7 | 7 | 14 | 1.00 |
| | | % | 11.7 | 17.5 | 14.0 | |
| *P* value | | | >0.05 | >0.05 | <0.05 | |
| Mean ± SD | | | 24.91±2.66 | 26.66±4.21 | 25.3.22 | >0.05 |

**Table 2.** Comparative mean levels of renal function parameters between study groups are calculated by student *t* test

| Serum values | Group | N | Mean | ±SD | *P* value |
|---|---|---|---|---|---|
| Urea (mg/dL) | Patients | 60 | 81.48 | 21.84 | <0.001 |
| | Healthy | 40 | 32.30 | 7.46 | |
| Creatinine (mg/dL) | Patients | 60 | 14.56 | 5.76 | <0.001 |
| | Healthy | 40 | 0.96 | 0.40 | |
| Uric acid (mg/dL) | Patients | 60 | 3.02 | 0.80 | <0.001 |
| | Healthy | 40 | 3.80 | 0.59 | |
| Albumin (g/dL) | Patients | 60 | 40.37 | 6.16 | <0.001 |
| | Healthy | 40 | 48.51 | 6.76 | |
| Total protein (g/dL) | Patients | 60 | 62.84 | 15.10 | >0.05 |
| | Healthy | 40 | 66.30 | 8.10 | |

**Table 3.** Comparative mean levels of lipid profile parameters between study groups are calculated by student t test

| Groups | | N | Mean | ±SD | *P* value |
|---|---|---|---|---|---|
| Cholesterol (mg/dL) | Patients | 60 | 160.15 | 32.53 | <0.001 |
| | Healthy | 40 | 139.67 | 29.06 | |
| HDL-c (mg/dL) | Patients | 60 | 32.78 | 13.51 | <0.001 |
| | Healthy | 40 | 44.92 | 11.35 | |
| LDL-c (mg/dL) | Patients | 60 | 89.76 | 28.86 | >0.05 |
| | Healthy | 40 | 88.71 | 18.61 | |
| TG (mg/dL) | Patients | 60 | 111.85 | 51.94 | >0.05 |
| | Healthy | 40 | 95.65 | 49.12 | |
| VLDL-c (mg/dL) | Patients | 60 | 23.13 | 10.44 | <0.05 |
| | Healthy | 40 | 20.63 | 10.54 | |

HDL, High density lipoprotein; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein; TG, Triacylglycerol

cohort study, CKD regression and mortality become more probable as individuals age, as opposed to CKD progression or kidney failure (17). From our study it has become apparent that kidney failure in older individuals (60 or older) has a high rate of regression as compared to kidney failure advancement. Regarding body mass index levels, the results do not demonstrate significant differences among BMI levels in patients and healthy individuals, except for those classified as underweight. Chronic kidney disease may potentially lead to a reduction in BMI among patients. It is worth noting that a negative correlation between CKD and BMI can be supported by the fact that CKD patients typically experience weight loss (18). The impairment of renal function decreases the capacity of glomerular filtration in the kidneys and results in an elevation of metabolic waste product levels in the plasma. Among these waste products, creatinine and urea are significant indicators for monitoring variations in renal function (19). Continuous monitoring of the blood levels of these metabolic byproducts during renal failure determines the need for dialysis (20). Renal failure patients exhibit higher levels of urea, uric acid and creatinine in their blood compared to healthy individuals. The defective kidney function and loss caused by renal failure lead to a reduced excretion of urea and creatinine from the body, causing their accumulation in the blood and subsequent increase in concentration (4,20,21). Our results indicate lower levels of albumin in patients with

**Table 4.** Comparative mean levels of serum ALP and ghrelin levels between study groups are calculated by student t-test

| Serum values | Groups | N | Mean | ±SD | *P* value |
|---|---|---|---|---|---|
| ALP (U/L) | Patients | 60 | 233.73 | 99.66 | <0.001 |
| | Healthy | 40 | 82.05 | 20.72 | |
| Ghrelin (ng/mL) | Patients | 60 | 0.23 | 0.73 | <0.001 |
| | Healthy | 40 | 0.80 | 0.46 | |

ALP, Alkaline phosphatase.

**Table 5.** Correlation relationships among variables and serum ghrelin (ng/mL) calculated by Pearson's correlation test

| Parameters in serum | | Ghrelin (ng/mL) |
|---|---|---|
| Creatinine (mg/dL) | Pearson's correlation | -0.129 |
| | *P* value | 0.325 |
| Urea (mg/dL) | Pearson's correlation | -0.256 |
| | *P* value | 0.048 |
| Uric acid (mg/dL) | Pearson's correlation | 0.023 |
| | *P* value | 0.864 |
| Cholesterol (mg/dL) | Pearson's correlation | -0.167 |
| | *P* value | 0.201 |
| HDL-c (mg/dL) | Pearson's correlation | 0.111 |
| | *P* value | 0.399 |
| LDL-c (mg/dL) | Pearson's correlation | -0.153 |
| | *P* value | 0.242 |
| TG (mg/dL) | Pearson's correlation | -0.242 |
| | *P* value | 0.063 |
| VLDL (mg/dL) | Pearson's correlation | -0.242 |
| | *P* value | 0.063 |
| Albumin (g/dL) | Pearson's correlation | 0.143 |
| | *P* value | 0.277 |
| Total protein (g/dL) | Pearson's correlation | 0.117 |
| | *P* value | 0.373 |
| ALP (U/L) | Pearson's correlation | -0.108 |
| | *P* value | 0.412 |

HDL, High density lipoprotein; LDL, Low density lipoprotein; VLDL, Very low density lipoprotein; TG, Triacylglycerol; ALP, Alkaline phosphatase enzyme.

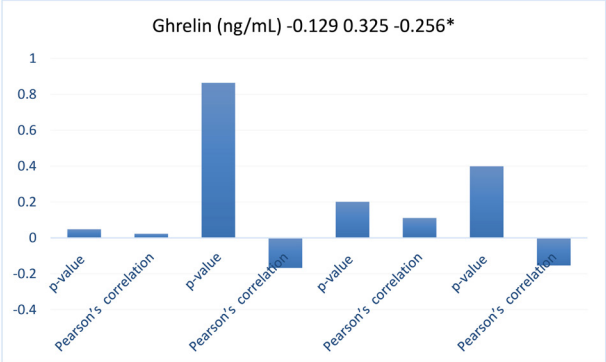


**Figure 1**. Correlation relationships among variables are calculated by Parson's correlation test.

renal failure compared to the control group. Previous research has shown that decreased plasma albumin levels in patients make CKD more prone to progress towards end-stage renal disease, and such patients should be closely monitored and provided with more aggressive treatment (22). Serum albumin levels have been found to be independently associated with proteinuria in patients with diabetic nephropathy (23). The findings of another study suggested that serum albumin levels are linked to the diagnosis of renal disease, therefore, measuring albumin levels may be beneficial for predicting the prognosis (24). The results of the levels of cholesterol and VLDL parameters in patients exhibited a significant increase in comparison to healthy subjects, whereas HDL-c in patients displayed a significant decrease in comparison to healthy subjects. The progression of CKD leads to alterations in lipid metabolism. The dysfunction of the kidney is accompanied by various disturbances in lipoprotein metabolism, which result in dyslipidemia and an increase in atherogenic particles (25), such as hypertriglyceridemia, elevated concentrations of LDL-c, and reduced levels of HDL-c (26). The alternations are connected to oxidative stress increase and a surge in cardiovascular mortality in CKD patients (27). Concerning cardiovascular problems, reduced kidney function is a dangerous factor because of the high extensiveness of dyslipidemia in patients (28). The results of this study suggest an uprise in the levels of ALP in patients compared to healthy people. Pyrophosphate contributes as an active inhibitor of calcification. ALP promotes the hydrolysis of pyrophosphate. Patients with end-stage renal disease, the connection between ALP and cardiovascular morbidity and mortality has been suggested, as they are at a high risk of vascular calcification due to increased levels of ALP (29). Numerous studies on CKD patients have demonstrated that elevated concentrations of ALP are associated with a high risk of cardiovascular events, and ALP has been established as an independent predictor of death and cardiovascular events (30,31). The concluded data of the study has revealed a downfall in the levels of ghrelin in patients compared to healthy controls, which is consistent with the proven fact that the use of exogenous ghrelin as a treatment increases renal protection through anti-oxidative mechanisms, by reducing mitochondrial reactive oxygen species levels (9). The findings have therefore confirmed that exogenous ghrelin treatment reduces oxidative damage by decreasing lipid peroxidation and subsequently increasing the activity of antioxidant enzymes, such as glutathione peroxidase and catalase (32,33). Hence, our data findings suggest a decrease in plasma ghrelin levels in renal failure patients, and ghrelin is negatively correlated with renal function. Serum ghrelin is also negatively correlated with urea. Therefore, a decrease in plasma ghrelin levels may serve as a potential indicator of kidney insufficiency in CKD.

## Conclusion

Data findings implicated serum ghrelin is negatively correlated with serum urea. Therefore, decreasing in plasma ghrelin level may be a probable indicator of kidney insufficiency in CKD.

## Limitations of the study

This study was conducted on a limited group of CKD

patient· We suggest further investigations on this aspect of hemodialysis patients by larger sample size and multi-centric studies.

## Authors' contribution

**Conceptualization:** Khalid Shaalan Sahab.
**Data curation:** Khalid Shaalan Sahab, Mohammed Asaad Mahdi.
**Formal analysis:** Khalid Shaalan Sahab, Ammar M. AL-Azzawi.
**Funding acquisition:** Mohammed Asaad Mahdi.
**Investigation:** Khalid Shaalan Sahab, Ammar M. AL-Azzawi.
**Methodology:** Khalid Shaalan Sahab, Mohammed Asaad Mahdi, Ammar M. AL-Azzawi.
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**Visualization:** Khalid Shaalan Sahab, Mohammed Asaad Mahdi.
**Writing–original draft:** Khalid Shaalan Sahab.
**Writing–review & editing:** Khalid Shaalan Sahab, Ammar M. AL-Azzawi.

## Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Diyala University College of Sciences donated their agreement to this study prior to any intervention (Ref; CEPEC/40). All volunteers donate written informed consent and authorization to include to the study.

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