The relation between dual energy x-ray absorptiometry measurement of body fat composition and plasma ghrelin in patients with end-stage renal disease

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ABSTRACT

الأهداف: توضيح دور «الجرلين» في إضطرابات سوء التغذية الملحوظة لدى مرضى الفشل الكلوي وعلاقته بتركيب الدهون في الجسم باستخدام جهاز دكسا (DXA).

الطريقة: شملت الدراسة 60 مريضاً. في المجموعة الأولى 30 مريض كلوي في المراحل النهائية يخضعون لغسيل كلى، و30 مريض كلي في مرحلة ما قبل الغسيل وتحت العلاج التحفظي، أما المجموعة الثانية فقد شملت 20 شخصاً سليماً. وقد أجريت هذه الدراسة في القصر العيني – القاهرة – جمهورية مصر العربية، خلال عام 2007م. وقد تم تقييم تركيب دهون الجسم الإجمالية، التباينية، وكتلة الجسم بواسطة جهاز دكسا (DXA). وقياس الجرلين في البلازما بواسطة "اليسا".

النتائج: وجدنا أن مستوي «الجرلين» في مرضى الغسيل الكلوي و ما قبل الغسيل الكلوي اعلي منه في الأصحاء، وأيضا أعلى في مرضي الغسيل الكلوي مقارنة بمرضى ما قبل الغسيل في مرضى الغسيل الكلوي كان مستوي الجرلين ذو علاقة عكسية مع الوزن، منسوب كتلة الجسم، وكتلة الدهون بالجذع، وعلاقة طردية مع الكرياتينين. أما في مرضي ما قبل الغسيل الكلوي كان مستوي الجرلين ذو علاقة عكسية مع الوزن، منسوب كتلة الجسم، وكتلة الدهون بالجذع، وعلاقة طردية مع الكرياتينين وكتلة الجسم. أما مجموعة الأصحاء، أظهر الجرلين علاقة عكسية مع الوزن، منسوب كتلة الجسم، كتلة الدهون بالجذع، كتلة الدهون بالجسم، وعلاقة طردية مع كتلة الجسم.

خاتمة: كان الجرلين مرتفع جدا في مرضي الكلي في مراحله النهائية مما قد يكون ناتجاً عن انخفاض استخراجه من الكلي. توجد دائما علاقة عكسية بين الجرلين وتركيب الدهون بالجسم في مرضي الغسيل الكلوي. تقوم دكسا (DXA) بقياس غير مخترق لتركيب الجسم بدقة عالية، لذلك يجب اعتماد قياس تركيب الجسم في مرضي الفشل الكلوي لتقييم حالتهم الغذائية.

Objectives: To clarify the role of ghrelin in malnutrition in uremia and its relationship to fat composition using dual x-ray absorptiometry (DXA).

Methods: This is a cohort study including Group I: 60 patients with end stage renal disease (30 on hemodialysis [group IA] and 30 pre-dialysis [group IB]) and Group II: 20 controls. This study was carried out in Cairo University Hospital, Kasr Al-Aini, Cairo, Egypt in 2007. Body fat composition (total, differential, and lean body mass) was assessed using DXA, and plasma ghrelin was measured.

Results: Ghrelin was significantly higher in hemodialysis and pre-dialysis groups compared to the control group, and higher in hemodialysis group compared to the pre-dialysis group. In hemodialysis, ghrelin was negatively correlated with weight, body mass index (BMI), and truncal fat mass, and positively correlated with serum creatinine. In pre-dialysis, ghrelin inversely correlated with weight, BMI, and truncal fat mass, and positively correlated with serum creatinine, lean body mass. In control, plasma ghrelin showed negative correlation with weight, BMI, truncal fat mass, and body fat mass, and positive correlation with lean body mass.

Conclusion: Ghrelin was markedly elevated in renal failure due to its decrease in excretion. Negative correlation between ghrelin and fat composition was detected in dialysis patients. Serial evaluation of body fat composition using DXA is recommended for assessment of nutritional status of those patients.

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End-stage kidney disease is a chronic condition associated with a high prevalence of nutritional dysfunction.[1] This malnutrition is resistant to intervention, and is a major predictor of morbidity and mortality in patients on hemodialysis (HD).[2,3] There is a linear correlation between body mass index (BMI) and survival in dialysis patients, to the extent that the usual association of increased mortality with obesity is reversed in patients who receive renal replacement therapy.[4,5] Nutritional parameters that have been correlated independently with increased mortality and morbidity include low serum albumin, and cholesterol.[6,7] Nakamoto et al[3] also found that hypoalbuminemia is a major predictor of morbidity and mortality in patients under HD. Recently, chronic inflammation was proposed to be an important predictor of outcome in dialysis patients. Inflammatory markers are commonly elevated in chronic renal failure, and levels of these seem to correlate with malnutrition, maintenance of residual renal function, and volume control.[8] Numerous studies suggest a strong association between nutrition and clinical outcome in chronic HD patients. While the determination of malnutrition is often based on objective measurements, such as biochemical parameters and anthropometric data, there is no single measurement that can reliably predict the risk for malnutrition, or poor outcome.[9] Understanding the physiology of energy metabolism and appetite regulation has much progressed, with the recent discovery of a number of important energy producing hormones, including ghrelin, resistin, and leptin.[10,11] Ghrelin is a novel 28-amino-acid octanoylated peptide, which act as an endogenous ligand for the growth hormone (GH) secretogogue receptor. Ghrelin is secreted into the blood stream primarily from endocrine cells within the stomach.[12] However, recent evidence suggests that other tissues also synthesize ghrelin, including the kidney.[13] Ghrelin has been reported to regulate feeding and body weight through the stimulation of the hypothalamic appetite centers, and coordination of energy balance so its dysregulation may be important in obesity.[14] Although its initial discovery was as a novel GH secretagogue, it has been found to regulate feeding behavior by modulating expression levels of orexigenic peptides in the hypothalamus.[14,15] Ghrelin also has several other physiological actions. It antagonizes leptin action, and promotes the production of orexigenic neuropeptides, such as neuropeptide Y, resulting in an increase in feeding, and body weight.[16] Indeed, peripheral infusion of ghrelin stimulates food intake in both rats and humans.[17] In general, loss of body fat mass and wasting due to cancer, cardiac cachexia, or anorexia nervosa is associated with elevated circulating levels of ghrelin.[18-20] Thus, it is unlikely that overproduction of ghrelin causes the obesity syndrome. Yoshimoto et al[21] reported 2.8 fold higher ghrelin levels in patients with renal failure. To elucidate the putative role of plasma ghrelin in the pathogenesis of malnutrition observed in uremia is the focus of the present study, and also to study its relationship to body fat composition using Dual x-ray absorptiometry (DXA). Dual x-ray energy absorptiometry was originally developed to examine bone mineral density, and examine the body in mm^3 dividing the human body in 3 parts: bone, fat and bone free (soft) tissue, and fat tissue. The European Society for Clinical Nutrition and Metabolism recommends DXA as a reference method in body composition studies.[22]

Methods. This study was performed for evaluation of the pathological differences between the 3 groups of patients: HD patients, pre-dialysis patients on conservative treatment, and healthy volunteers after obtaining an approval from the ethics committee in Cairo University Hospital, Kasr Elaini, Cairo, Egypt. The study was carried out in 30 hemodialysis patients (15 males and 15 females), age range 25-67 years old, and 30 patients (16 males and 14 females) with chronic renal failure (CRF) on conservative treatment. The age range was 24-68 years, and admitted to the hospital for kidney biopsy. All patients were recruited from the Dialysis Unit and Outpatient's Clinic of the hospital in 2007. The control group consisted of 20 age matched, gender, and body mass index (BMI) healthy subjects (10 males and 10 females), age range 23-64 years, without known disease, recruited mainly from the medical and paramedical staff. All patients and controls were informed about the aim of the study and we obtained their consent. All patients were clinically stable, their body weight was stable (<5% alteration of the body weight) for 6 months previous to enrolment, and there were no signs of clinically overt malnutrition. They were all free of acute illness, and no clinical or laboratory signs of infection, without uncontrolled hypertension, no oral contraception in women of childbearing age, and with normal liver function tests. None of the patients was receiving steroids, anticoagulants, or cytotoxic drugs. The exclusion criteria included pregnancy, in addition to the previously mentioned diseases and drugs. The following investigations were performed for all subjects; detailed history, physical examination, and anthropometric measurements including: BMI, calculated by weight (kg)/square of the height in meters. Following an overnight fasting (12 hours), we collected blood samples for estimation of hormonal, and general analytical data from all subjects. Plasma ghrelin level was measured using an enzyme linked immunosorbent assay (ELISA). The separated serum was used for determination of serum levels of albumin, calcium,

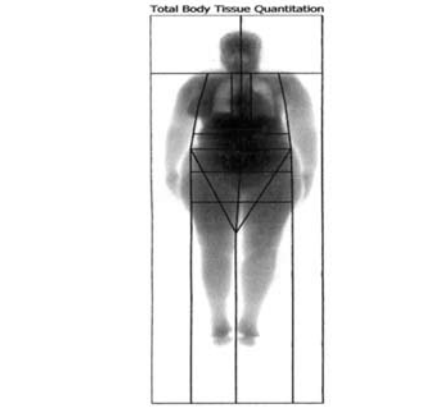
phosphorus, triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), and creatinine. Dual x-ray absorptiometry measurements for assessment of fat composition (Lunar Prodigy, GE, USA) were carried out to all participants. Before the start of everyday work, the technologist performs a quality control check according to the manufacturer's instructions. Total fat and lean tissues were calculated in grams, percentages of total, and differential body fat were also assessed, and this was carried out in reference to the matched age, weight (according to BMI), and gender.

Statistical Package for Social Science (SPSS) program version 9.0 was used for the analysis of the data. Data was summarized as mean ± SD. Student's t-test was used for the analysis of 2 quantitative data. Non-parametric test (Mann-Whitney U test) was used for the analysis of 2 qualitative data. One-way ANOVA was carried out for the analysis of more than 2 variables followed by post-hoc test for detection of significance. Simple linear correlation (Pearson's correlation for quantitative data, and Spearman correlation for qualitative data) was carried out to detect the relation between the ghrelin with all other demographic, and laboratory data. The correlative coefecient value was considered weak if the values are <0.25, mild if >0.25 to <0.5, moderate if >0.5 to <0.75 and strong if >0.75.[23] Stepwise multiple regression analysis was carried out for the detection of factors affecting ghrelin. A *p*-value of <0.05 is considered statistically significant.

Results. The main clinical characteristics and metabolic parameters (mean±SD) in hemodialysis patients, pre-dialysis patients, and control subjects are shown in **Table 1**. There was no significant difference between groups regarding age, weight, BMI, mean values of cholesterol, and LDL-c. However, patients on hemodialysis had significantly lower mean values of body fat mass, and lower mean values of lean body mass compared to the pre-dialysis, and control groups. When comparing pre-dialysis and control groups, the pre-dialysis group had significantly lower mean values of body fat mass compared to the control subjects. The mean levels of truncal fat mass, and body fat mass were significantly lower in both hemodialysis and pre-dialysis groups compared to control subjects, but there was no significant difference between hemodialysis and pre-dialysis groups in both parameters (**Figures 1 & 2**). The mean value of plasma ghrelin was significantly higher in patients with HD when compared to both pre-dialysis, and control subjects. Furthermore, the mean plasma ghrelin level was significantly higher in pre-dialysis patients compared to the control subjects (**Figure 3**). By using simple correlation analysis in the hemodialysis group, plasma ghrelin levels were inversely correlated with weight, BMI (**Figure 4**), and truncal fat mass (**Figure 5**), while it was positively correlated with creatinine. By using multiple regression analysis in the hemodialysis group, plasma ghrelin was shown to be dependent on the BMI (p=0.001) only. Regarding

Table 1 - The main clinical characteristics and metabolic parameters (mean ± SD) in hemodialysis patients, pre-dialysis patients, and control subjects.

Variables	Hemodialysis group Mean ± SD N= 23	Pre-dialysis group Mean ± SD N=20	Control group Mean ± SD N= 20	*P*-value
Age (years)	42.4 ± 13.1	43.3 ± 13.02	43.2 ±12.3	0.9
Weight (kg)	66.1 ±13.9	66.4 ± 13.2	66.3 ± 11.9	0.9
Body mass index (kg/m^2)	26.3 ± 5.6	26.9 ± 5.3	26.2 ± 4.8	0.9
Total cholesterol (mg/dl)	182.1 ± 27.7	191.6 ± 20.5	191.4 ± 19.5	0.3
Triacylglycerol (mg/dl)	139.9 ± 50.8^a	117.1 ± 23^b	114.1 ± 27.6^b	0.04*
HDL-c (mg/dl)	42.1 ± 4.3^a	47.9 ±6.3^b	49.1 ±6.3^b	0.001*
LDL-c (mg/dl)	115.2 ± 20.3	119.1 ±19	120.6 ±17.5	0.6
Calcium (mg/dl)	7.88 ± 1.23^a	8.46 ± 0.7^a	9.5 ± 0.9^b	0.001*
Phosphorus (mg/dl)	5.23 ± 1.54^a	4.41 ± 0.6^b	4.03 ± 0.4^c	0.001*
PTH (pg/ml)	480.6 ± 158.4^a	87.9 ± 11.8^b	66.5 ±16.7^c	0.001*
Albumin (g/dl)	4.2 ± 0.5^a	3.97 ± 0.5^a	4.49 ± 0.3^b	0.002*
Creatinine (mg/dl)	10.1 ± 2.7^a	4.11 ± 0.77^b	0.89 ± 0.1^c	0.001*
Ghrelin (ng/ml)	10.8 ± 3.7^a	5.1 ± 1.6^b	2.57 ± 1^c	0.001*
Truncal fat mass (%)	31.4 ± 10.45^a	32.1 ± 9.9^a	40.1 ± 9.6^b	0.02*
Body fat mass (%)	31.6 ± 11.1^a	32.1 ± 9.3^a	41.7 ± 8.5^b	0.005*
Lean body mass (gm)	39.9 ± 7.6^a	46.3 ± 11.4^b	46.5 ± 6.2^b	0.009*



Region	Tissue (fat %)	Centile	Total mass (kg)	Fat (g)	Lean (g)	BMC (g)
Left arm	47.6	-	-	2,112	2,328	139
Left leg	50.0	-	-	5,337	5,340	426
Left trunk	46.1	-	-	8,020	9,384	441
Left total	46.2	-	-	16,118	18,740	1,235
Right arm	47.5	-	-	2,053	2,266	141
Right leg	50.0	-	-	4,786	4,790	403
Right trunk	46.1	-	-	7,876	9,219	418
Legs	50.0	-	-	10,123	10,130	828
Trunk	46.1	-	-	15,896	18,603	858
Total	46.1	-	70.9	31,548	36,905	2,447

Figure 1 - Female patient, 54 years with renal impairment (predialysis) with high ghrelin level. The table showed different fat distribution. The total fat is 31.548 kg (46.1%), and truncal fat is 15.896 kg (46.1%).

the correlation between ghrelin and other variables in pre-dialysis patients, there was a significant negative correlation between plasma ghrelin and weight, and truncal fat mass, while there was a significant positive correlation between plasma ghrelin and creatinine, and lean body mass (**Figure 6**). By using stepwise multiple regression analysis in this group, plasma ghrelin was also shown to be dependent on weight only (p<0.005). The correlation between plasma ghrelin in the control subjects showed that the plasma ghrelin was inversely correlated with weight, BMI, truncal fat mass, and body fat mass, but positively correlated with creatinine. By stepwise multiple regression analysis, plasma ghrelin

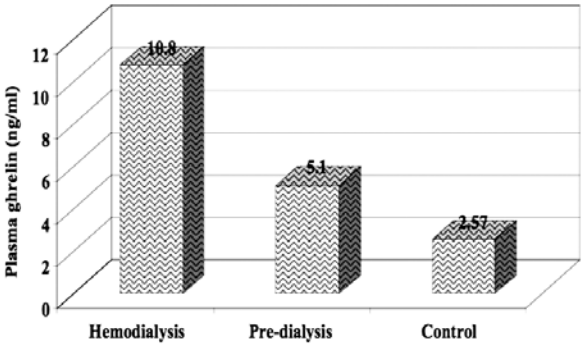


Figure 3 - Mean plasma ghrelin level in the studied groups.

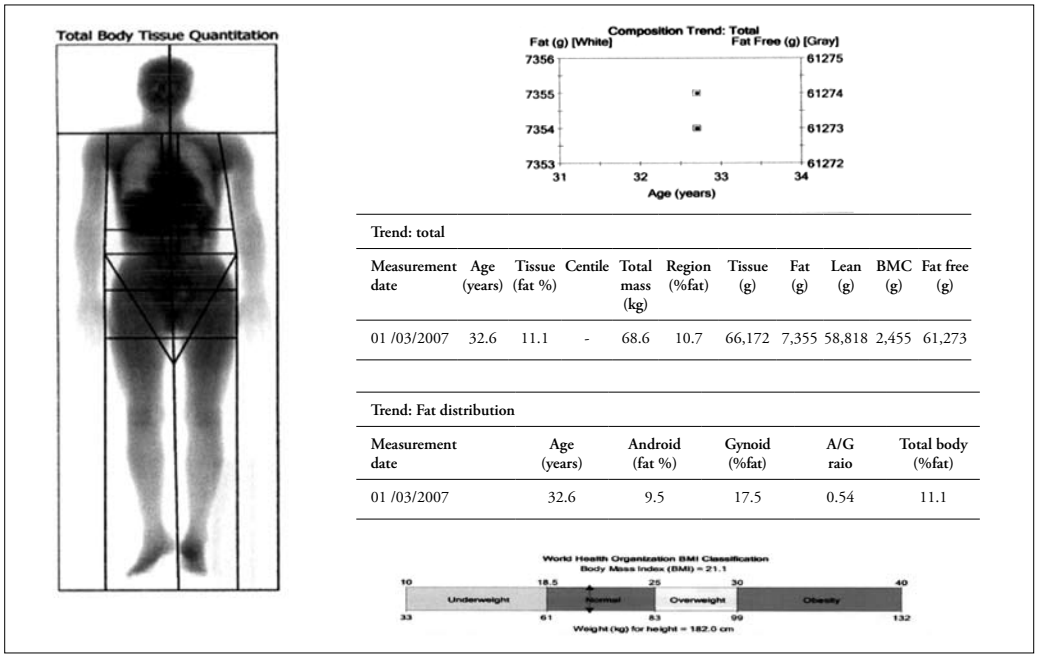


Figure 2 - Male patient, 32 years, renal failure on dialysis, high gherlin level, total tissue fat 7.355 kg (11.1%), truncal fat is 3.416 kg (10.4%).

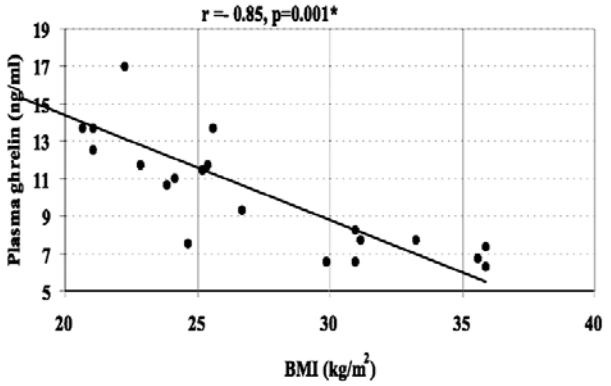


Figure 4 - Correlation between plasma ghrelin and body mass index in hemodialysis group.

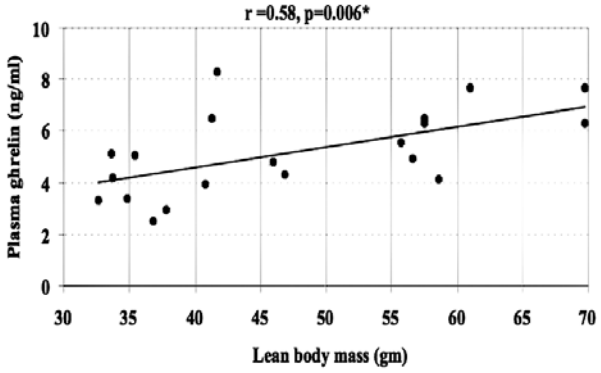


Figure 5 - Correlation between plasma ghrelin and lean body mass in pre-dialysis group.

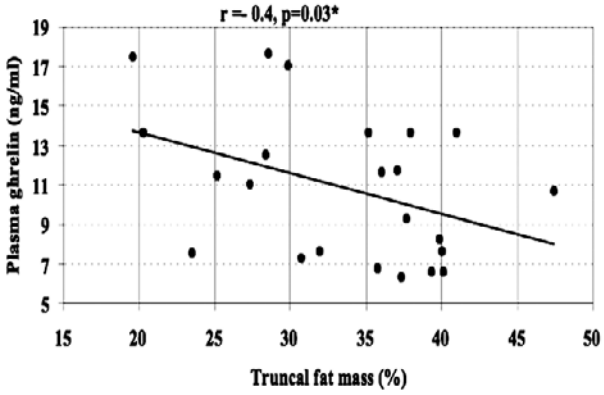


Figure 6 - Correlation between plasma ghrelin and truncal fat mass in the hemodialysis group.

was shown also to be dependent on truncal fat mass in this group (p=0.001).

Discussion. Anorexia in end-stage renal disease (ESRD) has many causes, which may include uremia per se, as well as, various co-morbidities and psychosocial factors. Malnutrition and loss of appetite are common symptoms in ESRD, and they are important predictors of prognosis.[24] The mechanism by which body fat contributes to the energy balance is unclear. Recently, several adipocyte (adiponectin, leptin, resistin), and gastric (ghrelin) peptides have been suggested to play a role in the regulation of energy balance.[25,26] The complementary roles of these hormones in the regulation of adipose tissue metabolism have not been examined simultaneously in ESRD. In this study there was no significant difference regarding age in the 3 groups, however, in a study conducted by Ohkawa et al,[27] they concluded that there is an association between age and decrease in muscle mass, as well as increase in visceral and intermuscular fat in non-diabetic HD patients. Such changes may be associated with the metabolic abnormalities, and increased mortality in elderly HD patients.[27] The current study showed lower mean total fat, and lean body mass in both hemodialysis and renal impairment groups than in controls. This is in agreement with Takahashi et al,[28] who postulated that DXA is a reliable method for body composition analysis in chronic hemodialysis patients.

The early detection of alterations in the body composition may provide an early indication of the development of malnutrition, and thus, serial evaluation of body composition using DXA should be valid for assessment of the nutritional status.[28] Other studies correlate different types of assessment of body composition, they found that DXA is superior to other simple methods for determining body composition like bioelectrical impedance analysis (BIA), and simple anthropometry, particularly when the emphasis is on repeated measurements.[29] Ghrelin is a recently described peptide hormone that is secreted by endocrine cells in the gastrointestinal tract,[10] is an endogenous ligand of the GH secretagogue receptor, and stimulates GH secretion.[30] It was suggested to be an important regulatory peptide in food intake, and long-term body weight regulation.[31,32] The present study demonstrated that plasma ghrelin levels were significantly higher in hemodialysis patients compared to the pre-dialysis group, and control subjects. Thus, the present results correspond to the findings of Yoshimoto et al,[21] suggesting that the kidney is an important site for clearance, and/or degradation of ghrelin. The

hypothesis proposed by Nagaya et al,[19] suggesting that the increased plasma ghrelin may represent a compensatory mechanism under conditions of extreme anabolic/catabolic imbalance. The present study also showed a positive correlation between plasma ghrelin and serum creatinine in hemodialysis patients, and even in patients with mild to severe renal impairment (pre-dialysis group). Similar results were obtained by Iglesias et al.[33] The increase in ghrelin levels after bilateral nephrectomy of approximately 3.1 times in mice would indicate that the kidney plays an important role in the clearance, or degradation of this hormone.[21] The observed negative correlations between plasma ghrelin and BMI, and truncal fat mass in the present study were in agreement with the study of Ayala et al,[34] who investigated patients with ESRD, and found markedly high plasma ghrelin concentrations in the hemodialysis group, and its level correlated negatively with the BMI, and truncal fat mass.

A relationship between ghrelin and adipose tissue has been reported. Ghrelin stimulates adipogenesis, and circulating ghrelin levels are reduced in obesity.[21] Patients with ESRD have reduced lifespan, a large percentage of patients with ESRD have traditional risk factors such as diabetes, hypertension, malnutrition, and abnormalities in cholesterol.[35] Malnutrition associated to uremia is characterized by loss of lean body mass with preservation of fat mass leading to absolute, or relative fat excess.[35] Previous study's examined the effect of ghrelin on food intake in chronic kidney disease patients. Nine peritoneal dialysis patients with mild-to-moderate malnutrition were given subcutaneous ghrelin, or saline placebo. The administration of subcutaneous ghrelin significantly increased mean absolute energy intake double fold in these patients, compared with placebo. These results indicate that subcutaneous ghrelin administration might improve nutrition.[36,37] There is resistance to ghrelin action in ESRD patients, either peripheral or central, or both. Duo to its significant correlation with the composition of body fat, ghrelin could modulate the metabolic substrate, and reduce fat utilization to maintain energy balance. Thus, ghrelin elevation in these patients is only a compensatory pathway rather than a causative factor.

There was one limitation in our study, which was the reduced number of control subjects compared to the total number of patients, due to insufficient number of volunteers who agreed to join the study, and give their consents.

In conclusion, plasma ghrelin concentration was markedly elevated in patients with ESRD, which might be caused by decreased excretion, or metabolism in the kidney during renal failure. Serial evaluation of body fat composition using DXA is a non invasive method that should be valid for assessment of the nutritional status of renal failure patients.

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