RESEARCH ARTICLE

Serum ghrelin levels: Is there any association with malnutrition and depression in peritoneal dialysis patients?

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Abstract

Background: Ghrelin is a physiologic regulatory hormone of appetite and body weight, and its concentrations increase in chronic kidney disease. This study aimed to analyze the effects of malnutrition and depression on the plasma ghrelin levels in peritoneal dialysis (PD) patients.

Methods/Patients: The relationship between fasting serum ghrelin concentration, type of dialysate solution, malnutrition-inflammation score (MIS), and depressive symptoms of 87 PD patients were analyzed. Depressive symptoms were evaluated using the Beck Depression Inventory.

Results: No significant relationship between ghrelin concentration and body mass index (BMI), MIS or depression scores was detected. The mean serum ghrelin concentration in patients using amino acid-based solutions was higher than in non-users ($p < 0.001$). The mean serum ghrelin concentration of the patients using icodextrin-based solutions was found to be significantly higher than non-users (8.69 ± 5.04 vs 6.61 ± 2.8 ng/ml respectively, $p = 0.02$). There was no significant difference in MIS between the patients in terms of amino-acid and/or icodextrin usage.

Conclusions: There is no association between BMI, MIS, and depression with ghrelin concentrations in PD patients. Icodextrin and/or amino acid-based solutions usage may increase the serum ghrelin concentration without a significant effect on BMI and measures of malnutrition. HIPPOKRATIA 2018, 22(1): 43-48.

Keywords: Ghrelin, malnutrition, Beck Depression Inventory, malnutrition-inflammation score, body mass index, peritoneal dialysis

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Introduction

Ghrelin is a 28-amino acid peptide secreted predominantly by the oxyntic cells of the stomach and plays an important role in the regulation of appetite and body weight. There are two major forms of circulating ghrelin: the acyl ghrelin (AG), with an n-octanoylated serine residue in position 3, and the des-acyl ghrelin (DAG)[1]. The active form is AG with orexigenic effect while DAG has anorexigenic effect[2]. In addition to its orexigenic properties, other functions of ghrelin include energy homeostasis, gastrointestinal, cardiovascular, pulmonary, and immune modulation, increased cell proliferation, and differentiation, and effects on bone physiology[3]. Ghrelin is mainly metabolized and excreted by the kidneys[4].

Plasma ghrelin and des-acyl ghrelin concentrations in patients with end-stage renal disease (ESRD) are higher than in the healthy population[4]. Endogenous ghrelin levels correlation was positively correlated with inflammatory markers in both chronic kidney disease (CKD)[5] and non-CKD patients[6,7]. Chronic inflammation is a significant cause of anorexia, malnutrition, and depression in uremic patients. It is possible that inflammation may affect ghrelin secretion and lead to stimulation of anorexia in these patients[8,9]. An increase in ghrelin concentration has been associated with chronic depression, anorexia, and malnutrition[10]. Development of malnutrition in ESRD is complex, and its etiology is multifactorial[8,9]. Anorexia and prolonged stress such as depression appear to be the leading causes of malnutrition in affected patients.

Ghrelin concentrations are known to be raised in peritoneal dialysis (PD) patients[11]. In a study measuring ghrelin concentrations following glucose absorption in PD patients, an increase in ghrelin concentration was reported to be inversely proportional to plasma insulin, leptin, and total body fat ratio compared to controls. Periodic intra-peritoneal instillation of glucose-based dialysate may alter ghrelin secretion through an effect on insulin secretion[12]. The aim of this study was to test the effect of malnutrition and depression on ghrelin concen-

tration and to evaluate the effects of different solutions on the ghrelin concentration in peritoneal dialysis.

Subjects and Methods

The study was designed as cross-sectional and observational, was conducted in the Peritoneal Dialysis outpatient clinic of Kocaeli University Hospital from 1/05/2013 until 30/07/2013, and was approved by the local Ethics Committee (KOU KAEK 2013/164, date: 04/06/2013). Informed consent was obtained from all participants prior to enrollment. Out of the 123 consecutive PD patients examined, we enrolled 87 PD patients who were willing to participate and were in follow-up for at least three months, according to our inclusion/exclusion criteria. We excluded eligible PD patients in the presence of an acute infection, chronic inflammatory disease, severe liver disease, history of malignancy, pregnancy, and patients younger than 18 years of age.

All patients were receiving four to five exchanges of between two and two and a half liters of glucose-based solutions, at concentrations of 1.36 %, 2.27 % or 3.86 %, daily. In addition, these glucose-based solutions were supplemented in some patients with amino acid and/or icodextrin-based combinations according to their total weekly urea clearance and ultrafiltration (UF) requirements.

All anthropometric measurements were performed while the peritoneal cavity was empty. Subcutaneous fat tissue evaluation was performed adjacent to the triceps muscles or at the mid-axillary line. Muscle wasting was evaluated by assessment of atrophy of deltoid and quadriceps muscles. Body mass index (BMI; body weight/height^2) of all patients was calculated. For comparisons, patients were divided into three groups according to their body weight into groups depending on BMI: normal (BMI: 18 to 24), overweight (BMI: 25 to 30), and obese (BMI >30).

Both the malnutrition-inflammation score (MIS) scale and the Beck depression inventory score (BECK) of all patients were assessed by the same investigator trained explicitly for this task. Patients were again divided into two groups: according to their MIS score: well-nourished (MIS ≥6) and malnourished (MIS <6) according to MIS values. Similarly, patients with BECK ≤17 were grouped as having no symptoms of depression while those with scores >17 were classified as having depressive symptoms. The daily volume of urine [residual renal volume (RRV)] was also used for stratification of patients into two groups with an arbitrary cut-off point of 200 ml.

Blood samples were drawn between 08:00 and 09:00, on the first day of the week, following at least eight hours of fasting and after the completion of the first exchange of the day. For the patients who were treated with automated PD (APD) their blood samples were taken two hours after they were separated from the machine at specified hours. In all samples, plasma albumin, total cholesterol, low-density lipoprotein (LDL), high density lipoprotein (HDL), total triglycerides, blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), hemoglobin (Hb), white blood cell count (WBC), alkaline phosphatase (ALP) sodium (Na), potassium (K), calcium (Ca), phosphorus (P), parathyroid hormone (PTH) concentration, and total iron binding capacity (TIBC) were measured. The cut-off values for the laboratory test results were evaluated according to the Kidney Disease Improving Global Outcomes (KDIGO) 2013 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[13-15]. The parameters for the evaluation of malnutrition, protein-energy wasting, depression, and BMI were adjusted according to the Nutrition in Chronic Renal Failure Guidelines of KDIGO, 2000 and Peritoneal Dialysis Adequacy Guidelines of KDIGO, 2006.

The patients were also divided into groups for comparison according to the hemoglobin (cut-off: 11 g/dl) and albumin concentration (cut-off: 4 g/dL)[13-16]. The mean albumin levels of the patients were 3.43 ± 0.51 gr/dl and for Hb was 10.6 ± 1.6 gr /dl. The decision for the cut-off values of Hb and albumin was made according to the KDIGO guidelines and the goals estimated by the department. A significant increase in the death risk was reported when the serum albumin level is below 4 gr/dl for HD patients and below 3.8 gr/dl for PD patients[16].

Weekly urea clearance (Kt/V) values, normalized to body fluid content, were used for dialysis adequacy. The patients' demographic characteristics and etiology of renal failure were also recorded. Samples for ghrelin measurement were collected into ethylenediaminetetraacetic acid (EDTA) containing tubes which were cooled to 4 °C, then immediately centrifugated at 3,500 rpm, and the supernatants were frozen at -40 °C until further analysis. Plasma ghrelin concentration was measured using an enzyme immunoassay (EIA) analyzer (Phoenix Pharmaceuticals, Burlingame, CA, USA) and a human ghrelin EIA kit (Dynex-DSX, Pewaukee, WI, USA) in micro enzyme-linked immunosorbent assay (ELISA) device. Plasma samples were re-warmed to room temperature, pipetted into the immunoplate wells, and incubated with primary antibody and biotinised peptide for two hours at room temperature. Then the wells were washed with assay buffer four times, added streptavidin-horseradish peroxidase (SA-HRP), and incubated at room temperature for one more hour. The wells were subsequently washed with assay buffer four times, and then TMB substrate solution was added and incubated for one hour at room temperature. As the reaction ended, NHCl was added into each well, and optical density measurements were made in the micro ELISA device at 450 nm wavelength, and the results were calculated according to the standard curves.

Statistical analysis

Before conducting the study, a sample size of 79 individuals was estimated to be sufficient to demonstrate a difference of ghrelin concentrations with 90 % power in correlation analysis[17]. All statistical analyses were performed using IBM SPSS for Windows, version 20.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the as-

sumption of normality. Normally distributed variables are expressed as mean ± standard deviation while the continuous variables that did not have normal distribution are expressed as median [interquartile range (IQR)]. Also, categorical variables were summarized as counts (percentages). Comparisons of normally distributed continuous variables between the groups were performed using the Student's t-test. For non-normally distributed continuous variables, differences between groups were tested using the Mann Whitney U-test. A two-sided p-value <0.05 was considered as statistically significant.

Results

The study population consisted of 87 (47 female and 40 male) PD patients with a mean age of 52.3 ± 12.7 years. The clinical characteristics of the patients and the etiology of CKD are given in Table 1. The mean time on the PD program was 48 ± 35 months. More than half of the patients (n =47; 54 %) had MIS ≥6 and were considered to have malnutrition while 28.7 % (n =25) had depressive symptoms with BECK ≥17.

Table 1: Demographic, clinical and analytical data of the 87 patients enrolled in this cross-sectional and observational study.

Demographics	
Age (years)	52.3 ± 12.7
Sex (M/F)	40/47
BMI (kg/m^2)	30.16 ± 7.20
Obese patients (BMI >30 kg/m^2)	26 of 87 patients
Diabetes (yes/no)	80/7
Hypertension (yes/no)	42/45
Cardiovascular disease (yes/no)	17/70
rhEPO therapy (yes/no)	42/45
Modality of peritoneal dialysis	
CAPD/APD (%)	90.8/9.2
Icodextrin	44 of 87 patients
Aminoacid-based solutions	18 of 87 patients
Analytical data	
Albumin (g/dl)	3.43 ± 0.51
Hemoglobin (g/dl)	10.6 ± 1.6
Dialysis parameters	
Duration(months)	48
Weekly Kt/V	2.63±1.16

Values are given in mean ± standard deviation, unless otherwise stated in brackets, CAPD: continous ambulatory peritoneal dialysis, APD: automated peritoneal dialysis, Kt/V: urea clearance.

The majority of the patients were on continuous ambulatory peritoneal dialysis (CAPD) (90.8 %) while the rest were on automated peritoneal dialysis (APD). Forty-four patients (50.6 %) were using icodextrin, and 18 (20.7 %) were using aminoacid-based solutions in addition to glucose-based PD solutions. The remainder 25 (28.7 %) patients were only using glucose-based solutions. There was a significant relationship in the usage of icodextrin-based together with amino acid-based solutions (p =0.02). There was no significant difference between the groups when the patients were divided according to their RRV (p =0.21). The median of UF was 1500 cc (IQR: 750 cc) in patients using icodextrin and amino acid solution while the median UF volume in non-using patients was 1000 cc (IQR: 1200 cc).

Mean BMI for the whole cohort was 30.16 ± 7.20. Twenty patients (23 %) were considered to have normal weight, 30 (34.5 %) were overweight, and 37 (42.5 %) were obese. The mean ghrelin concentration for the whole cohort was 7.66 ng/mL (min-max: 0.67-35.5 ng/ml). There was no significant difference in mean ghrelin concentrations between the groups when the patients were divided into groups by gender, age or BMI. However, mean serum ghrelin concentrations of patients using amino acids or icodextrin-based solutions were significantly higher than non-users (Table 2).

Although well-nourished patients (MIS ≥6) had higher mean serum ghrelin concentration (8.22 ng/ml), when compared with patients with MIS <6 the difference was

Table 2: Comparison of mean ghrelin levels between the groups, patients were divided into according to values of their body mass index, malnutrition-inflammation score, Beck Depression Inventory, Hemoglobin, residual renal volume, amino acid-based peritoneal dialysis, and Icodextrin-based peritoneal dialysis.

		n	Mean Ghrelin level ng/ml	SD	p value
BMI	<25	20	8.44	3.09	0.590
	≥25	67	7.43	4.47	
MIS	<6	40	6.99	1.95	0.155
	≥6	47	8.22	5.39	
BECK	<17	62	7.78	4.82	0.640
	≥17	25	7.32	1.98	
Hb (g/dL)	<11	45	7.68	3.07	0.650
	≥11	42	7.63	5.18	
RRV (cc)	<200	20	8.34	3.37	0.059
	≥200	67	7.46	4.42	
AA-based PD	NO	69	7.0	2.44	0.004
	YES	18	10.17	7.56	
Icodextrin-based PD	NO	43	6.61	2.8	0.020
	YES	44	8.69	5.04	

n: Number, BMI: body mass index, MIS: malnutrition-inflammation score, BECK: Beck Depression Inventory, Hb: Hemoglobin, RRV: residual renal volume, AA: amino acid, PD: peritoneal dialysis, SD: standard deviation.

not statistically significant (6.99 ng/ml, p =0.155). There was no significant difference between the MIS values of patients using amino acid or icodextrin-based solutions and non-users (p =0.277).

There was a statistically significant difference between normalized protein catabolic rate (nPCR) values of patients who were using icodextrin-based solutions and non-users (p <0.001). The nPCR median value for the patients using icodextrin-based solutions was 1.06 (0.81-1.68) gr/kg/day while for non-users it was 2.04 (1.26-2.5) gr/kg/day (p <0.001) (Table 3 and Table 4).

Patients classified as depressive had generally lower mean ghrelin concentration (7.32 ng/ml) compared to patients without depressive symptoms (7.78 ng/ml), but this difference was not statistically significant (p =0.64). When patients using and not using icodextrin and/or amino acid-based solutions were compared for either symptom of depression or albumin concentration, no significant difference was found (p =0.74 and p =0.365, respectively). In the current study, the more depressive patients were found to have worse MIS scores (p =0.034) but there was no correlation between albumin levels and depression (p =0.64).

Discussion

Several studies have demonstrated that plasma ghrelin levels are increased in patients with ESRD compared to normal individuals[4,7,11]. Obesity is associated with low ghrelin levels in uremic patients[10]. In cachectic patients, high plasma ghrelin levels are considered to be an adaptive response to chronic low caloric intake[18]. High ghrelin levels in cachexia are thought to be an adaptive response to chronic caloric deprivation.

Table 3: Comparisons of body mass index, Beck Depression Inventory, residual renal function and parameters of peritoneal equilibration test in patients using and not using icodextrin-based solutions.

Parameters	Patients using icodextrin -based solutions (n: 44)	Patients not using icodextrin -based solutions (n:43)	p value
BMI	29.65 (25.42-33.90)	28.80 (25-31)	0.33
BECK	10 (6-17)	9 (3-18)	0.81
Kt/V	2.23 (2-3.13)	2.47 (1.82-2.92)	0.39
nPCR (gr/kg/day)	1.06 (0.81- 1.68)	2.04 (1.26-2.5)	<0.001
Creatinine clearance (ml/min)	62.65 (50-98)	71.83 (49-110)	0.39
Residual GFR (ml/min)	6.75 (1.2-24)	10.97 (0.3-35)	0.76
Residual urine volume (cc)	550 (25- 1181)	700 (300-1400)	0.20
D/P crt	0.64 ± 0.11	0.65 ± 0.12	0.57

n: Number, Values are are expressed as median (interquartile range) or mean ± standard deviation, BMI: body mass index, BECK: Beck Depression Inventory, Kt/V: urea clearance, nPCR: normalized protein catabolic rate, D/P crt: dialysate-peritoneal creatinine ratio.

Table 4: Comparisons of body mass index, Beck Depression Inventory, residual renal function and parameters of peritoneal equilibration test in patients using and not using amino acid-based solutions.

Parameters	Patients using icodextrin -based solutions (n: 44)	Patients not using icodextrin-based solutions (n:43)	p value
BMI	28.64 (24.73-31.87)	29.1 (25-32)	**0.454**
BECK	10.5 (6-17.25)	9 (3.5-17)	**0.495**
Kt/V	2.43 (1.9- 3.06)	2.36 (1.94-3.1)	**0.859**
nPCR (gr/kg/day)	1.74 (1.04-1.89)	1.43 (0.81-2.31)	**0.71**
Creatinine clearance (ml/min)	71.31 (57.57-112.86)	68.80 (46.65-96.49)	**0.22**
Residual GFR (ml/min)	15.50 (3.17-61.62)	6.75 (1-30.58)	**0.19**
Residual urine volume (cc)	750 (112-1193)	600 (250-1200)	**0.82**
D/P crt	0.68 ± 0.132	0.64 ± 0.11	**0.25**

Values are are expressed as median (interquartile range) or mean ± standard deviation, BMI: body mass index, BECK: Beck Depression Inventory, Kt/V: urea clearance, nPCR: normalized protein catabolic rate, D/P crt: dialysate-peritoneal creatinine ratio.

In our study, the mean ghrelin level in PD patients was found to be approximately1.6 times higher than normal levels[11]. Evidence of malnutrition, which is an important mortality indicator, has been reported in as much as 54 % of ESRD patients in previous studies[19,20]. The role of ghrelin as a cause of anorexia and malnutrition in ESRD has been demonstrated in a study by Monzani et al[21]. Although we found higher ghrelin levels in the group with signs of malnutrition, the difference was not statistically significant compared to the well-nourished patients. In our study, there was no difference between MIS scores of patients regardless of whether they were using icodextrin or amino acid-based solutions.

The current literature concerning the relationship between malnutrition and depression is contradictory as some report a relationship while others did not find such a link[22-24]. It has been reported that depression causes a fall in serum albumin level and hence predisposes to malnutrition[23,24]. It is well recognized that malnutrition is common in CKD, secondary to elevated tumor necrosis factor and cortisol levels and impaired carbohydrate metabolism is essential for the maintenance of malnutrition[25]. In our study, there was a significant association between depressive patients and worse MIS values.

We found depressive symptoms in 28.7 % of PD patients which is similar to previous reports[26,27]. Depression in ESRD increases the morbidity by modifying the immunological and stress response, affecting the nutritional status, impairing treatment compliance and preventing access to medical care or renal replacement treatment[26,27].

In our study, the patients' BMI figures were generally high and homogeneously distributed. Lack of a significant correlation between BMI and ghrelin can be attributed to this homogeneous pattern. Similarly, there was no difference in depressive scores of patients in terms of amino acid or icodextrin-based solution usage.

There was no significant correlation detected between ghrelin concentration and Hb, albumin, and creatinine in the patients. A significant correlation between ghrelin and serum creatinine has been identified in only one study in the literature[4]. However, many researchers have found a significant correlation between ghrelin and albumin. In contrast, no significant correlation between Hb and ghrelin has been previously reported. We could not find a significant difference in ghrelin concentrations between the genders similar to earlier reports[4].

The effects of residual renal function (RRF) on ghrelin metabolism and clearance of ghrelin by HD or PD should be noted, and the evaluation of measurements should be interpreted accordingly. In our study, we measured only de-acylated ghrelin levels and the impact of PD on ghrelin concentration was neglected. Ghrelin concentrations were found to be significantly lower in patients with preserved RRF than those without RRF due to the key role that renal metabolism plays in the elimination of ghrelin[4].

Plasma ghrelin concentrations in PD patients are affected by multiple factors although the literature investigating this is scarce. Chang et al[28], in their study evaluating the effect of peritoneal permeability properties and dwell time of the PD solution on ghrelin concentration, demonstrated a positive correlation between peritoneal ghrelin clearance and dialysate-peritoneal creatinine ratio (D/P crt). Ayala et al, in their study of ghrelin in HD and PD patients, did not specify the properties of PD solutions and thus did not take into account the possible effects of different compositions on ghrelin levels[29].

There are studies in PD patients investigating concurrent plasma ghrelin and peptide YY levels following administration of glucose-based PD solutions[30]. They reported that both ghrelin and peptide YY were higher concentration than in a healthy population, but no significant rise in ghrelin levels was detected following oral glucose or high glucose content PD solutions. They did not evaluate the relationship and potential differences between ghrelin levels in patients doing nocturnal exchanges with icodextrin-based solutions neither.

The only study evaluating the effect of different PD solutions on ghrelin levels is that of Fontan et al who reported on the effects of different PD solutions on ghrelin concentrations[31]. In this study, the lactate-based PD solutions rich in advanced glycation end-products (AGE) were compared with new generation bicarbonate-based PD solutions containing lower levels of AGE over five weeks. The patients were assessed by peritoneal equilibration test (PET) scores and a range of biochemical parameters was assessed. These parameters were cytokine, adipokinin (leptin and adiponectin), and short-term appetite regulators which included ghrelin, peptide YY, cholecystokinin, and glucagon-like peptide 1 (GLP1). When both groups were compared there was no difference in the biochemical markers of peritoneal adequacy and permeability. However, adiponectin and acylated ghrelin concentrations were significantly higher in the group which used a lactate-based PD solution. There was no difference between the groups for other biochemical parameters measured.

In our study, the only significant difference in ghrelin concentrations was found between icodextrin and/or amino acid-based PD fluids users and non-users. The mean serum ghrelin concentration was significantly higher in patients using icodextrin and/or amino acid-based PD solutions. Although this result might be attributable to the increase in ghrelin reported in patients with malnutrition and ultrafiltration failure, lack of any significant relationship between ghrelin and malnutrition and ultrafiltration parameters in our patients might exclude this probability. There was no significant difference between icodextrin and amino acid-based solution users and non-users in terms of UF volume, albumin concentration, and BECK scores.

In addition to the biochemical properties of different PD fluids, permeability and other physiological characteristics of peritoneum will affect ghrelin concentrations in patients. In this study, there was no significant relationship between ghrelin concentrations and Kt/V, nPCR, and D/P crt values. The only difference between the users and non-users of icodextrin or amino-acid based solutions was found in nPCR which is a reliable marker of malnutrition in CKD. This difference in nPCR between our groups may

suggest the mechanism for the differences in mean ghrelin concentrations observed between these groups. Patients using icodextrin or amino-acid based solutions are likely to exhibit a worse nutritional status than non-users.

There are some weaknesses in this study. Firstly, the lack of a healthy control group for comparison is a flaw. Secondly, the fact that our patients were demographically and physically homogeneous that might be regarded as a bias confounding the comparison of factors influencing the ghrelin levels. Further experimental studies, adequately controlled and designed to evaluate the effects of different PD fluids on peritoneal membranes and plasma ghrelin concentration will provide a more in-depth insight into the metabolism of this peptide.

In conclusion, this study found no association between BMI, MIS, and depression with ghrelin concentrations in PD patients. Icodextrin and/or amino acid-based solutions usage may increase the serum ghrelin concentration without a significant effect on BMI and measures of malnutrition.

Conflict of interest

There is no conflict of interest.

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