Malnutrition Markers and Serum Ghrelin Levels in Hemodialysis Patients

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Objective. The aim of study was to investigate the changes levels of serum ghrelin in HD patients and its relationship to some malnutrition markers compared with healthy controls.

Methods. Forty-five patients on hemodialysis and forty healthy controls were studied. Biochemical parameters and serum ghrelin levels were measured. Both daily dietary intakes and body mass index (BMI) assessments were performed for evaluation of nutritional status.

Results. Ghrelin concentrations were significantly reduced in patients undergoing hemodialysis when compared to healthy controls (5±0.68 (1.1–18.5) pg/mL versus 7.8±0.84 (2.4–18.3) pg/mL; \( P = 0.004 \)). BMI and serum albumin in HD patients were markedly reduced compared to controls. The patients with an insufficient intake of energy and protein demonstrated slightly lower levels of serum ghrelin. A negative correlation between serum ghrelin concentration with age (\( r = −0.34, P = 0.02 \)), BUN (\( r = −0.26, P < 0.01 \)), and serum creatinine (\( r = −0.27, P < 0.01 \)) was observed in HD patients.

Conclusions. The findings suggest that decreased ghrelin levels in HD patients might be associated with anorexia. Further studies are needed to determine changes in serum ghrelin levels during dialysis and to clarify whether the decrease in ghrelin levels contributes to the malnutrition that is common in these patients.

1. Introduction

Protein-energy malnutrition and anorexia are common complications of uremia that occur frequently in renal failure patients [1–6]. The causes of malnutrition are not fully known. Some studies have reported that the accumulation of uremic toxic metabolites is one of the important factors [7]. The association between nutrition-regulating hormones and malnutrition is also important in HD patients [5, 6]. Ghrelin, one of the most potent orexigenic hormones, has been suggested as another possible mediator of anorexia in ESRD patients. This 28-amino acid hormone is produced largely in the stomach [1, 2, 6, 8–10]. Recent reports suggest that other tissues, including the kidney and brain, also synthesize ghrelin [9, 11]. Ghrelin is known to have multiple concurrent actions, including the anti-inflammatory effects [1, 12], release of growth hormone [2, 13, 14], fat accumulation, increased food intake, and stimulation of hypothalamic appetite centers [4, 9, 10, 13, 14]; thus it may help to regain appetite and struggle with malnutrition [1, 2, 4]. It is also involved in regulation of energy balance; thus, its dysregulation may induce obesity [6, 10, 13]. It is known that serum ghrelin level is strongly higher during fasting [8, 9, 15] and increases with weight loss [8]. It has been suggested that ghrelin to be cleared through the kidney and hemodialysis clears sufficiently ghrelin [9, 13]. Several researches compared ghrelin levels in patients treated with hemodialysis and healthy individuals that have reported conflicting results. Some studies found significantly increased ghrelin levels in HD patients [6, 9, 10, 13]. While Iglesias et al. [2] showed that patients undergoing HD had similar concentrations of ghrelin in comparison with the control group, Myrvang [16] reported that low ghrelin levels in dialysis patients increase...
mortality risk. In the study of Dötsch et al. [17], no effect of ghrelin on improving appetite and malnutrition was confirmed. However, the changes of serum ghrelin levels and its potential correlations with markers of nutritional status in hemodialysis patients are still incompletely characterized. This study investigated the changes levels of serum ghrelin in ESRD patients receiving dialysis treatment and its relationship to some malnutrition markers compared with healthy controls.

2. Material and Methods

In a cross sectional study, 45 ESRD patients undergoing hemodialysis (n = 20 males, n = 25 females, aged 43.2 ± 13.1 years), referred to Hemodialysis Center of Imam Ali and Khatam-Al-Anbia Hospitals, Zahedan, Iran, and 40 healthy subjects (n = 17 male, n = 23 female, aged 38 ± 12.6 years), matched for sex and age, were selected between February 2014 and May 2014. The patients underwent dialysis three times a week (each session 3-4 hours) for at least three months with a minimum Kt/V of 1.2. All participants were older than 18 years; none of them took the lipid-lowering medications and corticosteroids. During the previous three months they were not hospitalized or had not infectious and inflammatory diseases, diabetes mellitus, cardiovascular (CVD) and liver disease, thyroid, or cancer. The causes of ESRD included blood pressure (n = 16), kidney stone (n = 4), lupus erythematosus (n = 2), polycystic kidney (n = 4), glomerulonephritis (n = 8), and unknown (n = 11).

Dry body weight after dialysis and height were measured. Body mass index (BMI), as one of the markers of nutritional status, was evaluated based on the calculation of dry weight (Kg)/height (m²) [18, 19]. BMI was categorized in accordance with the recommendations of the World Health Organization [18]. Mean daily caloric and protein intake was expressed as mean ± SD and mean ± SEM with range and frequency, as appropriate. Variables with normal distribution were compared by Student’s t-test, one-way ANOVA. The differences among two groups after being categorized based on the BMI, serum albumin, and age were analyzed by 2-way ANOVA for repeated measures analysis of variance using Bonferroni test. Mann-Whitney U and Kruskall-Wallis tests were performed for nonnormal distribution variables. The variables associated with serum ghrelin levels were first evaluated by spearman correlation coefficient. The variables that significantly correlated with serum ghrelin were assessed as independent variables in the multiple regression analysis. A P value < 0.05 was considered significant.

4. Results

Demographic and nutritional parameters of subjects are demonstrated in Table 1. The patients underlying hemodialysis had markedly lower weight (P < 0.0001) and BMI (P < 0.001) than control subjects.

Table 2 describes chemical parameters and ghrelin levels in both groups. Serum albumin levels and hemoglobin were significantly reduced (P < 0.0001), and BUN, serum creatinine (P < 0.0001), and uric acid (P = 0.007) levels were markedly increased when compared to healthy controls (P < 0.0001). No significant difference was found between patients and controls for serum lipid profile levels. Ghrelin concentration was significantly declined in HD patients when compared to healthy controls (5 (1.1–18.5) pg/mL versus 7.8 (2.4–18.3) pg/mL; P = 0.004).

Table 3 demonstrates ghrelin levels based on malnutrition markers in both groups. Bonferroni’s multiple comparison test revealed that the levels of serum ghrelin were significantly lower in overweight/obese patients with BMI ≥ 25 kg/m² (5.2 (1.1–16.1) versus 8 (3.3–18.3); P < 0.01) and nonobese patients with BMI < 25 kg/m² (4.9 (1.1–18.5) versus 7.8 (2.4–16.9); P < 0.05) compared to control subjects. The levels of this peptide in patients with BMI less than 25 kg/m² were modestly lower when compared to obese patients (P > 0.05).

Older patients (>50 years old) had moderately (not significant) lower serum ghrelin levels compared to those with...
Table 2: Chemical parameters of HD patients and controls.

| Groups variables | HD patients (n = 45) | Controls (n = 40) | P$	ext{v}$ |
|------------------|---------------------|------------------|-----------|
| BUN (mg/dL)      | 60.4 ± 24.5         | 12.8 ± 3.3       | 0.0001    |
| Uric acid (mg/dL)| 6.3 ± 1.7           | 5.7 ± 1.5        | 0.007     |
| Creatinine (mg/dL)| 8.7 ± 3.6           | 0.78 ± 0.18      | 0.0001    |
| Cholesterol (mg/dL)| 168 ± 79            | 169 ± 42.6       | NS        |
| LDL-C (mg/dL)    | 82.3 ± 24           | 82.3 ± 23.7      | NS        |
| HDL-C (mg/dL)    | 42.4 ± 14.3         | 42.7 ± 12.4      | NS        |
| Triglyceride (mg/dL)| 129 ± 81.6         | 119 ± 79.4       | NS        |
| Albumin (g/dL)   | 3.4 ± 0.4           | 4.5 ± 0.76       | 0.0001    |
| Sodium (mmol/L)  | 141 ± 12            | 139 ± 10         | NS        |
| Potassium (mmol/L)| 5 ± 0.6            | 4.7 ± 0.9        | NS        |
| Calcium (mg/dL)  | 8.7 ± 11            | 9 ± 1.4          | NS        |
| Phosphorus (mg/dL)| 5.2 ± 1.4          | 4.9 ± 1.1        | NS        |
| Hemoglobin       | 10 ± 2.3            | 13.7 ± 1.9       | 0.0001    |
| *Ghrelin (pg/mL) | 5 ± 0.68            | 7.8 ± 0.84       | 0.004     |

Data were expressed as mean ± SD.
BUN: blood urea nitrogen; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein.
*Ghrelin level was reported as mean ± SEM and range because the data were not normally distributed.
NS: not significant.

Table 3: Serum ghrelin levels based on body mass index (BMI), age, and serum albumin levels in HD patients and controls.

| Groups variables | HD patients (n = 45) | Control (n = 40) | P$	ext{v}$ |
|------------------|---------------------|------------------|-----------|
| BMI (Kg/m$^2$)   |                    |                  |           |
| < 25             | 4.9 (1.1-18.5)      | 7.8 (2.4-16.9)   | 0.01      |
| (n = 34)         | (n = 20)            |                  |           |
| ≥ 25             | 5.2 (1.1-16.1)      | 8 (3.3-18.3)     | 0.04      |
| (n = 11)         | (n = 20)            |                  |           |
| P$	ext{v}$      | 0.17                | 0.5              |           |
| Age (yrs)        |                    |                  |           |
| < 50             | 5.8 (1.1-18.5)      | 7 (2.4-18.3)     | 0.06      |
| (n = 27)         | (n = 25)            |                  |           |
| > 50             | 3.8 (1.1-15.6)      | 6.5 (3.5-10.2)   | 0.17      |
| (n = 18)         | (n = 15)            |                  |           |
| P$	ext{v}$      | 0.055               |                  |           |
| Albumin          |                    |                  |           |
| < 3.5            | 3.8 (1.2-9.7)       | —                |           |
| (n = 5)          | (n = 0)             |                  |           |
| > 3.5            | 6.1 (1.1-18.5)      | 7.8 (2.4-18.3)   | 0.001     |
| (n = 40)         | (n = 40)            |                  |           |
| P$	ext{v}$      | 0.04                |                  |           |

less than 50 years and control subjects (3.8 (1.1-15.6) versus 5.8 (1.1-18.5); P = 0.055 and 7 (2.4-18.3); P = 0.06, resp.).

Serum ghrelin levels were markedly lower in patients with serum albumin < 3.5 g/dL than patients with serum albumin > 3.5 g/dL and controls (3.8 (1.2-9.7) versus 6.1 (1.1-18.5) (P < 0.04) and versus 7.8 (2.4-18.3), (P < 0.001), resp.), but no significant differences were observed between patients with serum albumin > 3.5 g/dL and control subjects.

When obese and nonobese patients were analyzed separately, energy (kcal/day), protein, and fat (g/day) intakes were markedly lower in both patient groups than controls (1321.5 ± 168 versus 1839 ± 587 kcal/day; P < 0.001 and 1267 ± 550 versus 1659 ± 665 kcal/day; P < 0.001) (54 ± 29 versus 84 ± 32 g/day; P < 0.001 and 59 ± 21.6 versus 83.6 ± 25 g/day; P < 0.001) and (45.5 ± 19 versus 61 ± 32 g/day; P < 0.05 and 41 ± 20 versus 54.5 ± 29 g/day; P < 0.05, resp.), as described in Table 4.

A negative correlation between serum ghrelin concentration with age (r = −0.34, P = 0.02), BUN (r = −0.26, P < 0.01), and serum creatinine (r = −0.27, P < 0.01) was observed among HD patients. Multivariate regression analysis demonstrated a significant negative correlation between serum ghrelin levels with age ($\beta = −0.269, P = 0.02$). In the multivariate model, serum albumin level as dependent variable correlated with BUN ($\beta = −0.492, P < 0.01$) and creatinine ($\beta = −0.557, P < 0.01$) (Table 5).

5. Discussion

We studied serum ghrelin levels in renal failure patients undergoing dialysis in comparison to healthy controls. Our data demonstrated a significantly decreased serum ghrelin level in ESRD patients treated by hemodialysis, which might be attributed to the kidney dysfunction in synthesizing it. On the other hand, the dialysis also degrades and/or is clear of ghrelin [9, 13]. This result is in accordance with Myrvang [16] study but incompatible with those of other studies which have previously been described in renal failure patients [2, 3, 6, 25, 26].

Table 4: Food intakes in HD patients and controls.

| Parameters | Regression coefficient (beta) | P$	ext{v}$ |
|------------|-------------------------------|-----------|
| Ghrelin    | Age                           | −0.269    | 0.02 |
| Albumin    | BUN                           | −0.492    | 0.01 |
| Creatinine |                               | −0.557    | 0.01 |

Data were expressed as mean ± SD.
*P < 0.001 HD patients versus controls.
*P < 0.05 HD patients versus controls.

Table 5: Multivariate regression analysis between serum ghrelin and albumin levels with various parameters in HD patients.

- **Energy (Kcal/day)**: $\beta = −0.557, P = 0.02$.
- **Carbohydrate (g/day)**: $\beta = −0.492, P < 0.01$.
- **Protein (g/day)**: $\beta = −0.557, P < 0.01$.
- **Fat (g/day)**: $\beta = −0.269, P = 0.02$.

Regression coefficient ($\beta$): $P < 0.01$. 
Regression coefficient ($\beta$): $P < 0.001$. 
Regression coefficient ($\beta$): $P < 0.05$.
In addition, uremic toxins including BUN and creatinine are also important factors which are associated with anorexia in these patients [7, 10]. A negative correlation observed between serum ghrelin and albumin levels with BUN and creatinine in this study, suggesting that high level of uremic toxin metabolites may lead to decreased serum ghrelin level or impair ghrelin's function, causes anorexia and malnutrition in these patients.

The limitations of our study were small sample size, lack of longitudinal data, and failure to measure the levels of protein catabolic rate (PCR), metabolic acidosis, bicarbonate, and chloride, which may also affect appetite and possibly the level of ghrelin in HD patients.

6. Conclusion

The findings suggest that decreased ghrelin levels in HD patients might be associated with high anorexia. However, this study could not explain the likely role of ghrelin in low food intake. Further studies are needed to determine changes in serum ghrelin levels during dialysis and to clarify whether the decrease in ghrelin levels contributes to the malnutrition that is common in these patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] W. W. Cheung and R. H. Mak, “Ghrelin in chronic kidney disease,” International Journal of Peptides, vol. 2010, Article ID 567343, 7 pages, 2010.
[2] P. Iglesias, J. J. Diez, M. J. Fernández-Reyes et al., “Serum ghrelin concentrations in patients with chronic renal failure undergoing dialysis,” Clinical Endocrinology, vol. 64, no. 1, pp. 68–73, 2006.
[3] M. Szczepańska, K. Szpyrner, B. Mazur, D. Zwolińska, K. Kiliś-Pstrusińska, and I. Makulska, “Plasma ghrelin levels in children with chronic renal failure on peritoneal dialysis,” Peritoneal Dialysis International, vol. 27, no. 1, pp. 61–66, 2007.
[4] H. Suzuki, A. Asakawa, H. Amitani, N. Nakamura, and A. Inui, “Ghrelin and cachexia in chronic kidney disease,” Pediatric Nephrology, vol. 28, no. 4, pp. 521–526, 2013.
[5] A. Aguilera, A. Cirugeda, R. Amaier et al., “Ghrelin plasma levels and appetite in peritoneal dialysis patients,” Advances in Peritoneal Dialysis, vol. 20, pp. 194–199, 2004.
[6] M. Pérez-Fontán, F. Cordido, A. Rodriguez-Carmona, J. Peteiro, R. García-Naveiro, and J. García-Buela, “Plasma ghrelin levels in patients undergoing haemodialysis and peritoneal dialysis,” *Nephrology Dialysis Transplantation*, vol. 19, no. 8, pp. 2095–2100, 2004.

[7] K. L. Johansen, K. Mulligan, V. Tai, and M. Schambelan, “Leptin, body composition, and indices of malnutrition in patients on dialysis,” *Journal of the American Society of Nephrology*, vol. 9, no. 6, pp. 1080–1084, 1998.

[8] H. Ariyasu, K. Takaya, T. Tagami et al., “Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans,” *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 10, pp. 4753–4758, 2001.

[9] A. Yoshimoto, K. Moris, A. Sugawara et al., “Plasma ghrelin and desacyl ghrelin concentrations in renal failure,” *Journal of the American Society of Nephrology*, vol. 13, no. 11, pp. 2748–2752, 2002.

[10] E. R. Ayala, R. Pecois-Filho, O. Heimbürger, B. Lindholm, L. Nordfors, and P. Stenvinkel, “Associations between plasma ghrelin levels and body composition in end-stage renal disease: a longitudinal study,” *Nephrology Dialysis Transplantation*, vol. 19, no. 2, pp. 421–426, 2004.

[11] K. Moris, A. Yoshimoto, K. Takaya et al., “Kidney produces a novel acylated peptide, ghrelin,” *FEBS Letters*, vol. 486, no. 3, pp. 213–216, 2000.

[12] D. Mafra, N. E. Farage, J. C. Lobo et al., “Relationship between total ghrelin and inflammation in hemodialysis patients,” *Peptides*, vol. 32, no. 2, pp. 358–361, 2011.

[13] K.-D. Nüsken, M. Gröschl, M. Rauh, W. Stöhr, W. Rascher, and J. Dötsch, “Effect of renal failure and dialysis on circulating ghrelin concentration in children,” *Nephrology Dialysis Transplantation*, vol. 19, no. 8, pp. 2156–2157, 2004.

[14] K. Wynne, K. Giannitsopoulou, C. J. Small et al., “Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial,” *Journal of the American Society of Nephrology*, vol. 16, no. 7, pp. 2111–2118, 2005.

[15] D. E. Cummings, R. S. Frayo, C. Marmonier, R. Aubert, and D. Chapelot, “Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues,” *American Journal of Physiology—Endocrinology and Metabolism*, vol. 287, no. 2, pp. E297–E304, 2004.

[16] H. Myrvang, “Risk factors: low ghrelin levels in dialysis patients increases mortality risk,” *Nature Reviews Nephrology*, vol. 7, no. 3, article 123, 2011.

[17] J. Dötsch, K. Nüsken, M. Schroth, W. Rascher, and U. Meißner, “Alterations of leptin and ghrelin serum concentrations in renal disease: simple epiphenomena?” *Pediatric Nephrology*, vol. 20, no. 6, pp. 701–706, 2005.

[18] L. K. Mahan, S. Escott-Stump, and J. L. Raymond, *Krause’s Food & the Nutrition Care Process, (Krause’s Food & Nutrition Therapy)*, WB Saunders, Elsevier, Philadelphia, Pa, USA, 13th edition, 2012.

[19] A. D. F. Barros, C. Moraes, M. B. S. Pinto, J. C. Lobo, and D. Mafra, “Is there association between acyl-ghrelin and inflammation in hemodialysis patients?” *Jornal Brasileiro de Nefrologia*, vol. 35, no. 2, pp. 120–126, 2013.

[20] H. Şahin, F. Uyanık, N. İnanç, and O. Erdem, “Serum zinc, plasma ghrelin, leptin levels, selected biochemical parameters and nutritional status in malnourished hemodialysis patients,” *Biological Trace Element Research*, vol. 127, no. 3, pp. 191–199, 2009.

[21] A. R. Qureshi, A. Alvestrand, A. Danielsson et al., “Factors predicting malnutrition in hemodialysis patients: a cross-sectional study,” *Kidney International*, vol. 53, no. 3, pp. 773–782, 1998.

[22] C. Y. Chen, A. Asakawa, M. Fujiyima, S. D. Lee, and A. Inui, “Ghrelin gene products and the regulation of food intake and gut motility,” *Pharmacological Reviews*, vol. 61, no. 4, pp. 430–481, 2009.

[23] D. E. Cummings and M. H. Shannon, “Roles for ghrelin in the regulation of appetite and body weight,” *Archives of Surgery*, vol. 138, no. 4, pp. 389–396, 2003.

[24] T. Itoh, N. Nagaya, M. Yoshikawa et al., “Elevated plasma ghrelin level in overweight patients with chronic obstructive pulmonary disease,” *The American Journal of Respiratory and Critical Care Medicine*, vol. 170, no. 8, pp. 879–882, 2004.

[25] T. Shiya, M. Nakazato, M. Mizuta et al., “Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion,” *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 1, pp. 240–244, 2002.

[26] M. Muscaritoli, A. Molfino, M. G. Chiappini et al., “Anorexia in hemodialysis patients: the possible role of des-acyl ghrelin,” *American Journal of Nephrology*, vol. 27, no. 4, pp. 360–365, 2007.

[27] R. Refael, A. Aguilerã, A. Circuégã et al., “Ghrelin plasma levels and appetite in peritoneal dialysis patients,” *Peritoneal Dialysis International*, vol. 24, supplement 2, p. 24, 2004.

[28] A. Asakawa, A. Inui, M. Fujiyima et al., “Stomach regulates energy balance via acylated ghrelin and desacyl ghrelin,” *Gut*, vol. 54, no. 1, pp. 18–24, 2005.

[29] T. Masaoka, H. Suzuki, H. Hosoda et al., “Enhanced plasma ghrelin levels in rats with streptozotocin-induced diabetes,” *FEBS Letters*, vol. 541, no. 1–3, pp. 64–68, 2003.

[30] A. E. Rigamonti, A. I. Picelli, and B. Corra, “Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients,” *Journal of Endocrinology*, vol. 146, pp. 241–244, 2002.