

# Study of Serum Levels of Leptin, C-Reactive Protein and Nutritional Status in Hemodialysis Patients

Farzaneh Montazerifar<sup>1</sup>; Mansour Karajibani<sup>2,\*</sup>; Zahra Hassanpour<sup>3</sup>; Mahla Pourmofatteh<sup>3</sup>

<sup>1</sup>Department of Nutrition, Pregnancy Health Research Center, School of Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran

<sup>2</sup>Department of Nutrition, Health Promotion Research Center, School of Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran

<sup>3</sup>Department of Nutrition, School of Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran

\*Corresponding Author: Mansour Karajibani, Department of Nutrition, Health Promotion Research Center, School of Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran. Tel: +98-9153414358, Fax: +98-5433295728, E-mail: mkarajibani@yahoo.com

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**Background:** Leptin is secreted by adipose tissue and decreases appetite. However, the role of leptin in the pathogenesis of hemodialysis (HD)-related malnutrition has not been fully evaluated.

**Objectives:** The aim of study was to investigate the association between the serum leptin levels, serum C-reactive protein (CRP) levels, and nutritional status in hemodialysis patients.

**Patients and Methods:** This analytical descriptive study included 45 hemodialysis patients and 40 healthy subjects. Biochemical parameters and serum leptin levels were measured. The nutritional status was evaluated using a food frequency questionnaire (FFQ) and the calculation of the body mass index (BMI).

**Results:** Serum leptin ( $P < 0.05$ ) and albumin ( $P < 0.0001$ ) levels and BMI ( $P < 0.001$ ) of HD patients were significantly lower, while CRP levels were significantly higher than those of controls ( $P < 0.0001$ ). HD patients consumed the lower daily servings of the food groups compared to the control subjects ( $P < 0.0001$ ). A significant positive correlation between serum levels of leptin and albumin and BMI was demonstrated. No significant correlations were identified between leptin level, CRP level, and other variables.

**Conclusions:** The findings suggest that low levels of leptin may be a contributory factor for malnutrition in HD patients. Further studies are required to ascertain the significance of leptin levels in relation to nutritional factors in hemodialysis patients.

**Keywords:** Serum Leptin; CRP; Hemodialysis Patients; Nutritional Status

## 1. Background

Malnutrition is common in patients with end stage renal disease (ESRD) on hemodialysis (HD). This may be associated with insufficient dietary intake, medication, inflammation, and/or their uremia status, which contribute to anorexia (1-4). Loss of appetite reduces the intake of dietary energy and other nutrients and leads to weight loss and malnutrition progression (4). Nevertheless, uremic toxins stimulate disorders of the central nervous system and adipose tissue (2), which may affect diminished appetite (2, 5, 6). Leptin, "a negative acute phase protein," is secreted by adipose tissue and acts on the hypothalamus in order to regulate food intake and energy expenditure (2, 3, 7). Leptin reduces body weight via neuronal activity modulation within the hypothalamus (8). It has been postulated that leptin plays an important role in inducing anorexia and malnutrition in uremic patients (2), but the mechanisms by which it affects progressive malnutrition in kidney failure and its clinical significance are not clearly un-

derstood (3). Conflicting results have been published about the relationship between serum leptin level and ESRD. Several studies have reported that serum levels of leptin are significantly increased in patients with chronic renal failure (3, 9). In a recent study, leptin level in a HD patient was not significantly different from the control (2). Some studies demonstrated that the high serum levels of C-reactive protein (CRP) and cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) elevate leptin gene expression (3, 4, 10), which may, in turn, play a role in inhibiting appetite during acute inflammatory conditions in renal failure patients (11, 12). In other studies, no correlation was identified between leptin level and body weight or nutritional status (4, 13, 14).

## 2. Objectives

Since data on the relationship between serum leptin

and nutritional status in hemodialysis patients are limited, the present study was performed to investigate the association between serum leptin and CRP levels and some nutritional factors in hemodialysis patients.

### 3. Patients and Methods

Forty-five patients with ESRD (20 male and 25 female subjects, aged  $43.2 \pm 13.1$  years) who were referred to the hemodialysis center of the Imam Ali teaching hospital, which is affiliated to the Zahedan University of Medical Sciences (Zahedan, Iran), were enrolled in this analytical descriptive study. All of the patients were dialyzed three times a week (each session lasting 3 - 4 hours) for at least three months with a minimum Kt/V of 1.2. A group of 40 healthy subjects (17 male and 23 female subjects, aged  $38 \pm 12.6$  years), who were matched for sex and age, were selected as controls during a medical visit to the internal clinic. The study was performed between February 2014 and May 2014.

All participants were older than 18 years old. None of them were prescribed with lipid-lowering medications and corticosteroids. The participants were not hospitalized or diagnosed with any infectious and inflammatory diseases, diabetes mellitus, cardiovascular (CVD), liver, thyroid diseases, or cancer, in the past 3 months immediately prior to study enrollment.

#### 3.1. Determination of Nutritional Status

The nutritional status of the subjects was evaluated using both the food frequency questionnaire (FFQ) and the calculation of the body mass index (BMI).

Specialized dietitians designed the FFQ. The FFQ's reliability and validity as well the fewest intakes of daily serving of the various food groups represented in the Food Guide Pyramid have been reported previously (15).

Body weight and height were measured in the control group after 12 hours of fasting, and after hemodialysis in HD patients. The BMI was calculated using the formula, weight (kg)/height (m<sup>2</sup>). BMI was categorized in accordance with the recommendations of the world health organization (16). A BMI  $< 18.5$  kg/m<sup>2</sup> was considered as a sign of malnutrition.

#### 3.2. Biochemical Analysis

After fasting overnight, blood samples were collected from all healthy subjects and patients immediately before HD. Biochemical parameters including serum levels of blood urea nitrogen (BUN), uric acid, creatinine, total cholesterol, triglyceride, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and albumin were measured with standard techniques by an automatic analyzer. Serum CRP concentrations were analyzed through enzyme immunoassay.

Serum leptin levels were assessed using commercial ELI-

SA (Enzyme Linked Immunosorbent Assay) kit (Human Leptin ELISA kit, (Biovendor [Cat No: RD191001100], USA). The serum samples were immediately frozen at  $-70^{\circ}\text{C}$  until analysis.

This study was approved by the ethics committee of Zahedan university of medical sciences (approval date 4 January 2014, number 6697). All subjects gave their informed consent for participation in the study.

#### 3.3. Statistical Analysis

The analysis was carried out using the SPSS statistical software package program (version 18 for windows, Chicago, USA). Data were expressed as mean  $\pm$  SD and mean  $\pm$  SEM with range, as appropriate. Variables with normal distribution were compared using the Student's t-test. Mann-Whitney U test was performed for non-normally distributed variables. Correlations among leptin and different parameters were determined using the Spearman's correlation coefficient. A P value of  $< 0.05$  was considered significant.

### 4. Results

Demographic and biochemical parameters of the HD patients and control group are exhibited in Table 1. Serum leptin ( $16.3 \pm 2.7$  ng/mL vs  $23 \pm 5.2$  ng/mL;  $P < 0.05$ ) and albumin ( $3.4 \pm 0.4$  g/dL vs  $4.5 \pm 0.76$  g/dL;  $P < 0.0001$ ) levels and BMI ( $22 \pm 2.1$  kg/m<sup>2</sup> vs  $24.7 \pm 4.9$  kg/m<sup>2</sup>;  $P < 0.001$ ) of HD patients were significantly lower, whereas serum CRP ( $11.1 \pm 2.4$  mg/L vs  $2.4 \pm 0.17$  mg/L;  $P < 0.0001$ ), BUN ( $60.4 \pm 24.5$  vs  $12.8 \pm 3.3$ ;  $P < 0.0001$ ), creatinine ( $8.7 \pm 3.6$  vs  $0.78 \pm 0.18$ ;  $P < 0.0001$ ), and uric acid ( $6.3 \pm 1.7$  vs  $5.7 \pm 1.5$ ;  $P < 0.01$ ) levels were higher than those in the control subjects. No significant differences in the lipid profile and blood pressure ( $P > 0.05$ ) readings were observed between the patients and controls. The causes of ESRD were hypertension ( $n = 16$ ), kidney stone ( $n = 4$ ), lupus erythematosus ( $n = 2$ ), polycystic kidney disease ( $n = 4$ ), glomerulonephritis ( $n = 8$ ), and unknown ( $n = 11$ ).

As shown in Table 2, HD patients consumed less daily servings of the food groups compared to controls except for bread and cereals ( $P < 0.0001$ ).

There was positive correlation between serum levels of leptin and BMI ( $r = 0.52$ ,  $P < 0.0001$ ) (Figure 1) and Albumin ( $r = 0.71$ ,  $P < 0.05$ ) (Figure 2).

Serum leptin levels were not significantly correlated with CRP level ( $r = 0.11$ ,  $P = 0.46$ ), age ( $r = 0.22$ ,  $P = 0.14$ ), duration of dialysis ( $r = 0.21$ ,  $P = 0.16$ ), systolic blood pressure ( $r = 0.02$ ,  $P = 0.91$ ), diastolic blood pressure ( $r = 0.07$ ,  $P = 0.64$ ), and serum levels of BUN ( $r = 0.11$ ,  $P = 0.45$ ), creatinine ( $r = -0.095$ ,  $P = 0.53$ ), uric acid ( $r = 0.24$ ,  $P = 0.11$ ), cholesterol ( $r = 0.05$ ,  $P = 0.72$ ), LDL ( $r = 0.09$ ,  $P = 0.55$ ), HDL ( $r = -0.18$ ,  $P = 0.24$ ), and triglycerides ( $r = 0.03$ ,  $P = 0.86$ ).

**Table 1.** Comparison of the baseline characteristics and chemical parameters between the HD patients and the control group <sup>a,b</sup>

| Variable                     | HD Patients (n = 45)    | Control (n = 40)    | P Value |
|------------------------------|-------------------------|---------------------|---------|
| Age, y                       | 43.2 ± 13.1             | 38 ± 12.6           | NS      |
| Gender, Male/Female          | 20/25                   | 17/23               |         |
| Dry weight, kg               | 55.5 ± 14.4             | 71.6 ± 17           | 0.0001  |
| BMI, kg/m <sup>2</sup>       | 22 ± 2.1                | 24.7 ± 4.9          | 0.001   |
| <b>Blood pressure, mmHg</b>  |                         |                     |         |
| Systolic                     | 124.2 ± 11              | 122 ± 10.5          | NS      |
| Diastolic                    | 79.3 ± 9.2              | 80.1 ± 7.8          | NS      |
| Duration of dialysis, months | 38.5 (3 - 96)           | -                   | -       |
| 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           | 0.01    |
| 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                 | 82.2 ± 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  |
| CRP <sup>c</sup> , mg/L      | 11.1 ± 2.4 (1 - 56)     | 2.4 ± 0.17 (1 - 4)  | 0.0001  |
| Leptin <sup>c</sup> , ng/mL  | 16.3 ± 2.7 (0.3 - 56.1) | 23 ± 5.2 (1.5 - 55) | 0.05    |

<sup>a</sup> Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NS, not significant.

<sup>b</sup> The values are presented as mean ± SD.

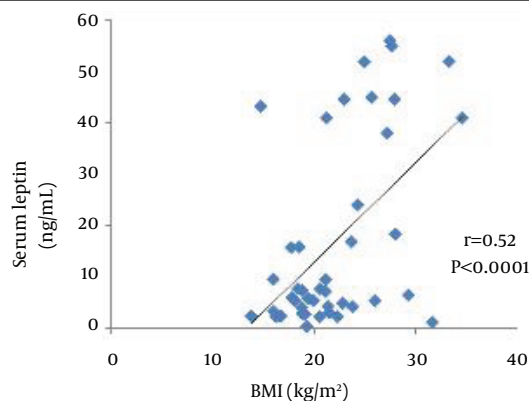
<sup>c</sup> CRP and leptin levels were reported as mean ± SEM and range because the data were not normally distributed.

**Table 2.** Comparison of The Food Pattern Intake Among Hemodialysis (HD) Patients and Controls <sup>a</sup>

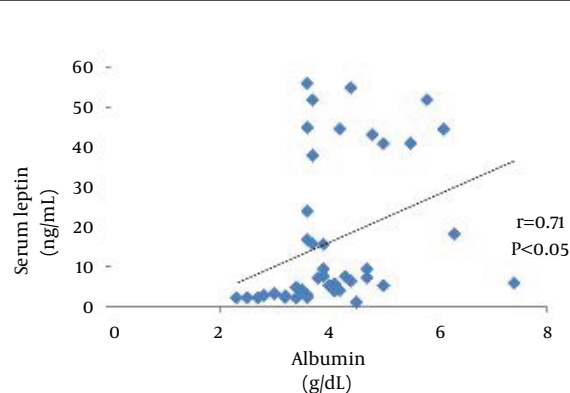
| Food groups (servings)  | HD Patients (n = 45) | Control (n = 40) | P Value         |
|-------------------------|----------------------|------------------|-----------------|
| Bread and cereals       | 8 ± 1.3              | 8.7 ± 1.7        | NS <sup>b</sup> |
| Milk and dairy products | 0.7 ± 0.02           | 3 ± 0.9          | 0.0001          |
| Fruits                  | 0.9 ± 0.2            | 3.2 ± 1          | 0.0001          |
| Vegetables              | 1.2 ± 0.3            | 4 ± 1.3          | 0.0001          |
| Meat, legumes and egg   | 2.2 ± 0.8            | 3.2 ± 1.2        | 0.01            |

<sup>a</sup> The values are presented as mean ± SD.

<sup>b</sup> NS, Not significant.



**Figure 1.** Correlation Between Serum Levels of Leptin (ng/mL) and BMI (kg/m<sup>2</sup>) in HD Patients



**Figure 2.** Correlation Between Serum Levels of Leptin (ng/mL) and Albumin (g/dL) in HD Patients

## 5. Discussion

Protein energy malnutrition (PEM) is common in renal failure patients and progresses during the dialytic stage. Mechanisms causing malnutrition in uremia are complex (1, 3, 17). To date, many studies have demonstrated that insufficient weight gain, hypoalbuminemia, inflammation as well as calorie and protein metabolism disorders and low food intake are important markers, which are strongly associated with mortality risk in hemodialysis patients (1-4, 6, 18). However, there have been few published studies on the relationship between serum leptin and nutritional factors in patients with chronic renal failure. Thus, the objective of this study was to assess serum leptin level and its relationship with some nutritional factors in hemodialysis patients. In the present study, body weight and BMI of HD patients were significantly lower than those of controls, similar to previous studies (1, 19). Serum albumin is also one of the other nutritional factors, which is sensitive to changes in nutritional intake (16). In our study, albumin level was markedly lower than controls. Some studies in HD patients have demonstrated a potential relationship between malnutrition and hypoalbuminemia, which depends on both nutrition and inflammation (1, 3, 17, 20, 21). The excretion of albumin into the urine due to impaired renal function (16) and its leakage via the dialysis membrane are also independent factors that affect serum albumin level (1). Some studies have suggested that leptin may be associated with anorexia and protein energy loss that are frequently observed in patients with end-stage renal disease (3, 17). In this study, the mean serum leptin level was significantly decreased in HD patients, particularly in subjects with BMI < 18.5 kg/m<sup>2</sup> and serum albumin level < 3.5 g/dL. Additionally, serum leptin levels were found to positively correlate with BMI and serum albumin levels. Similar data were previously obtained in other studies (2, 3, 22), while several studies showed varying results. In some studies, no correlation was found between serum leptin levels and changes in body weight (12-14, 19, 23) and serum albumin (4) in patients with renal failure. In several reports, a positive correlation between the body fat value, especially abdominal fat accumulation "as a source of pro-inflammatory adipokine," and serum leptin has been demonstrated in HD patients (24, 25). Inadequate food intake is also recognized as one of the important causes of malnutrition in hemodialysis patients (20, 26). Earlier studies have reported that a majority of uremic patients undergoing hemodialysis suffer from nutritional disorders (1, 2, 4, 20). Similarly, in the present study, patients consumed lower daily servings of milk and dairy products, fruit and vegetable compared to the control group, which might be associated with restriction of potassium and phosphorous intake in HD patients (27). However, our previous findings also indicated that the intake of energy and protein was significantly decreased in HD patients compared to that in the control group (28). Leptin is one of the pituitary appetite regulating peptides,

and its levels generally change in renal failure patients (3, 11, 12). It has been suggested that the low levels of serum leptin may lead to a reduced appetite during hemodialysis treatment (2). However, the role of leptin in regulating nutritional intake and energy expenditure has not been fully characterized. In our study, no correlation was found between leptin level and nutrient intake in HD patients, in agreement with earlier studies (4, 13, 14).

C-reactive protein (CRP) is a positive acute phase protein and can be increased with any kind of infection/inflammation (1, 3). Since increased serum CRP inhibits the serum albumin generation in hemodialysis patients (1), it may be a powerful determinant for anorexia, hypoalbuminemia, and the diagnosis of malnutrition in renal failure patients (1, 3, 21). Similar to our study, Sanjay et al. (3) reported that the mean CRP levels in HD patients was higher than the upper limit of normal, while some patients with high leptin levels had low CRP.

Although inflammatory marker levels are clearly increased in HD patients, this may be related to the exposure of blood to bioincompatible dialysis membranes (17). Other causes, including dietary and behavioral factors, cardiovascular diseases (29), and high serum leptin levels (10, 12) are also associated with an increase in CRP levels. In recent years, the association between inflammation and serum leptin levels in dialysis patients has been established. Some studies have reported that inflammatory process may contribute to the stimulation of leptin mRNA, which leads to an increase in the circulating leptin levels (10, 12). The findings of the present study demonstrated that although the patients with elevated CRP levels had markedly increased leptin concentration compared to patients with normal CRP, this was similar to control subjects (data not shown). However, no correlation was found between serum levels of CRP with leptin and other nutritional factors, suggesting that CRP is a poor predictor of malnutrition in dialysis patients. The limitations of our study included the small sample size and lack of longitudinal data.

The findings suggest that low levels of leptin may contribute to malnutrition in HD patients. Further studies are required in order to ascertain the significance of leptin in relation to nutritional factors in hemodialysis patients.

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## Authors' Contributions

Supervisor: Farzaneh Montazerifar. Advisor: Farzaneh Montazerifar, Mansour Karajibani. Data collection: Zahra Hassanpour, Mahla Pourmofatteh. Drafting of the manuscript: Farzaneh Montazerifar, Mansour Karajibani.



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