Serum CRP and Leptin Levels to Assess Nutritional Status in Patients on Maintenance Hemodialysis

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ABSTRACT

Introduction: Malnutrition is common in patients with End Stage Renal Disease (ESRD) on Hemodialysis (HD). Depending on the parameter measured, the prevalence of malnutrition in the chronic dialysis population ranges from 10 to 54%. It is related with the secretion of a number of proteins (adipokines), including leptin and adiponectin and also cytokines such as IL-6. This study was planned with the aim of reviewing the association of nutritional status with serum leptin and CRP levels in hemodialysis patients.

Material and methods: The present study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital from August 2017 to March 2019; consisted of 50 patients of End stage Renal Disease on maintenance hemodialysis admitted in Chattrapati Shivaji Subharti Hospital during the time period.

Results: Out of the 50 subjects, 35 (70%) were male and 15 (30%) were females. The Lean Body Mass (%) in the study subjects was 59.76±5.92. The overall mean leptin level distribution among the subjects was 1.51±0.36. The overall mean CRP level distribution among the subjects. was 3.75±0.47. A positive correlation was found between CRP and BMI with statistical significance as $p<0.05$ (table 11). Similarly a highly positive correlation was found between Leptin and BMI as $p<0.01$.

Conclusion: Our study point to possible use of serum leptin and CRP concentration as an indicator of nutritional status in HD patients based on observed significant positive correlation between serum leptin and CRP concentrations with BMI values.

Keyword: ESRD, Leptin, CRP.

INTRODUCTION

Chronic kidney disease is a patho-physiological process with multiple aetiologies, which leads to a gradual and a usually permanent loss of kidney function over time.[1] End-stage renal disease (ESRD) is a major healthcare problem worldwide, especially in developing countries. Protein and calorie (energy) malnutrition is common in patients with end-stage renal disease and is a powerful predictor of morbidity and mortality in this population.[2,3] Depending on the parameter measured, the prevalence of malnutrition in the chronic dialysis population ranges from 10 to 54%.

Adipose tissue is a complex organ, with pleiotropic functions beyond the mere storage of energy. It is related with the secretion of a number of proteins (adipokines), including leptin and adiponectin and also cytokines such as IL-6. Today, we know that adipose tissue plays an important role in the production of these molecules in the catabolic uraemic medium through its influence on systemic inflammation and uraemic anorexia.[4]

Serum leptin is increased in CKD and may be responsible for the anorexia–malnutrition syndrome.[5,6] However, other studies show that malnutrition in renal failure may be due to chronic inflammatory process reflected by increase in CRP.[7] LEPTIN-mainly produced by adipocytes; in general population is regarded as major regulator of body weight since it induces decrease of food intake and increases energy expenditure and weight loss. Leptin is cleared from the circulation by the kidney through both glomerular filtration and metabolic degradation in the renal tubules. Several recent studies have demonstrated that serum leptin concentrations are increased in patients with chronic kidney disease (CKD) and those on hemodialysis (HD). Reports from those studies suggest that elevated leptin levels in patients with damaged kidney function are primarily due to reduced renal filtration and metabolism.[8] Studies have shown that in patients with chronic renal failure, TNF–α and IL-1 are major pro-inflammatory cytokines, whereas IL-6 appears to be key mediator of acute phase reactant synthesis, including C-reactive protein (CRP).[9]

CRP (C-reactive protein): CRP is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. Inflammation is also one of the contributory factors for malnutrition.[5] An elevated serum CRP is reported in 20-65% of ESRD patients. Studies conducted so far have shown that increased CRP levels reflect presence of chronic inflammation in HD patients.[10] Earlier study by Stenvenkel[11] summarized the prevalence of elevated CRP levels from several investigations and concluded that more than 50% of HD patients had increased serum CRP concentration. Due to paucity of studies that demonstrate the effect of serum leptin and CRP on nutritional status in patients with

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ESRD on hemodialysis in India, this study was planned with the aim of reviewing the association of nutritional status with serum leptin and CRP levels in hemodialysis patients.

MATERIAL AND METHODS

The present Prospective observational study was conducted on 50 subjects for 2 years in the Department of Medicine at Chattrapati Shivaji Subharti Hospital from August 2017 to March 2019.

The study group consisted of 50 patients of End stage Renal Disease on maintenance hemodialysis admitted in Chattrapati Shivaji Subharti Hospital during the time period. Patients were enrolled in the study after obtaining written informed consent from parents and approval from Institutional Ethical Committee. Person between the age of 18-60 years were included in the study. All patients were put on detailed history, clinical examinations to fulfil the inclusion and exclusion criteria. Anthropometric and investigations were done among the included subjects.

Inclusion criteria: All patients of End Stage Renal Disease on maintenance hemodialysis with age 18-60 years.

Exclusion criteria:

- Age less than 18Years
- Age more than 60Years
- Patients of Acute Kidney Injury (AKI)
- Pregnant women
- Patients of any thyroid disorder
- Patient taking medication for weight reduction
- Patients of any chronic illness like inflammatory arthritis, vasculitis

Case selection

The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, socioeconomic status, medical history and previous history of taking any medications and supplements.

Ethical clearance

The study protocol for all procedures was approved by the Institutional Review Board for Ethical Clearance of Chattrapati Shivaji Subharti Hospital and was performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration of Helsinki of 1975, as revised in 2000. All patients were asked to sign a written consent form prior to commencement of the study.

Anthropometric tests: following anthropometric tests was performed:

(a) Standing height with bare feet was measured accurately to nearest 0.5 cm.

(b) Body weight was recorded with an "Avery" weighing scale accurately to within 50 g.

(c) Body surface area (BSA) in square meter (m2) was calculated from the height and weight using "Dubois" formula.

$$BSA\ (m^2) = Wt\ (kg)^{0.425} \times Ht\ (cm)^{0.725} \times 0.007184$$

(d) Lean body mass (LBM)/body fat estimation is the difference between total body mass (weight in kg) and weight of the body fat. It can be derived from the following formula:

$$\text{Lean Body Weight (men)} = (1.10 \times \text{Weight (kg)}) - 128 \times (\text{Weight}^2/(100 \times \text{Height (m)})^2)$$

$$\text{Lean Body Weight (women)} = (1.07 \times \text{Weight (kg)}) - 148 \times (\text{Weight}^2/(100 \times \text{Height (m)})^2)$$

(e) BMI in kg/m2 was calculated from total body mass (M, i.e., weight in kilograms) and height (H in meters) using the formula BMI (kg/m2) = M/(H × H).

Investigations: The following parameters were determined: hemoglobin, urea, sodium, potassium, C-reactive protein (CRP) and leptin levels.

Haemoglobin: The normal ranges for hemoglobin depend on the age and, beginning in adolescence, the gender of the person. The normal ranges are:

- Newborns: 17 to 22 gm/dL
- One (1) week of age: 15 to 20 gm/dL
- One (1) month of age: 11 to 15 gm/dL
- Children: 11 to 13 gm/dL
- Adult males: 14 to 18 gm/dL
- Adult women: 12 to 16 gm/dL
- Men after middle age: 12.4 to 14.9 gm/dL
- Women after middle age: 11.7 to 13.8 gm/dL

Urea: In general, around 7 to 20 mg/dL (2.5 to 7.1 mmol/L) is considered normal. But normal ranges may vary, depending on the reference range used by the lab, and your age.

Sodium: A normal blood sodium level is between 135 and 145 milliequivalents per liter (mEq/L).

Potassium:. The normal potassium level in the blood is 3.5-5.0 milliEquivalents per liter (mEq/L).

C-reactive protein (CRP): C-reactive protein (CRP) is one of the most sensitive acute-phase reactants for inflammation. Lab values vary, and there is no standard at present. However, in general, the results is reported in either mg/dL or mg/L. Levels in the 0.3 mg/dL to -1 mg/dL are considered mild and are usually seen with diabetes, hypertension (HTN), periodontitis, sedentary lifestyle, cigarette smoking, and many other non-inflammatory processes. In general, significant inflammation or infection is considered present at levels greater than 1 mg/dL.

Leptin levels: Concentration of leptin in serum was determined using the Invitrogen Hu Leptin ELISA kit (the sensitivity of the assay was 3.5 pg/ml; intra- and inter-assay coefficient of variations for lowest and highest values were 3.0 and 3.8% and 3.9 and 4.6%, respectively) while the levels of sOb R were assayed by Quantikine sOb R ELISA kit of R&D systems (the sensitivity of the assay was 0.057 ng/ml; intra- and inter-assay coefficient of variations for lowest and highest values were 6.1 and 4.9% and 8.6 and 6.8%, respectively).

STATISTICAL ANALYSIS

Data was collected in structured data collection forms. All the findings and observations were coded and entered in Excel master sheet and analysed discriptively.

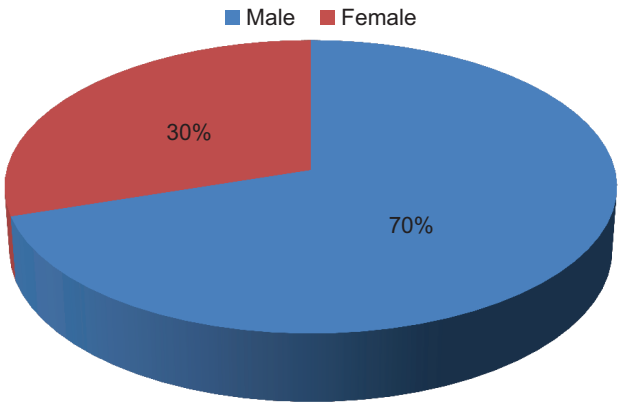
RESULTS

The present study was conducted in the department of Medicine at Chattrapati Shivaji Subharti Hospital from August 2017 to March 2019. The study group comprised of 50 patients of End stage Renal Disease on maintenance hemodialysis admitted in Chattrapati Shivaji Subharti Hospital during the time period.

Out of the 50 subjects, 35 (70%) were male and 15 (30%) were females as shown in graph 1.

The Lean Body Mass (%) in the study subjects was 59.76±5.92. Mean Lean Body Mass (%) in male and female subjects was 62±6.13 and 56±5.59 respectively. The overall Hb in the study subjects was 11.58±1.36.

The mean leptin level distribution among the male subjects in the present study was 1.54±0.38. The mean leptin level distribution among the female subjects was 1.45±0.29. The overall mean leptin level distribution among the subjects was 1.51±0.36 as shown in table 3.



Graph-1: Gender distribution of study subjects.

Gender	Mean Urea	Std. Deviation
Female	142.87	21.98
Male	149.23	20.27
Total	147.32	20.78

Table-1: Urea distribution among study subjects.

Gender	Lean Body Mass (%)	Std. Deviation
Female	56	5.59
Male	62	6.13
Total	59.76	5.92

Table-2: Lean body mass among study subjects

Gender	Mean Leptin	Std. Deviation
Female	1.45	0.29
Male	1.54	0.38
Total	1.51	0.36

Table-3: Leptin level distribution among study subjects.

Gender	Mean CRP	Std. Deviation
Female	3.73	0.57
Male	3.79	0.43
Total	3.75	0.47

Table-4: CRP level among study subjects.

Variables	CRP and BMI
r value	0.36
p value	0.01*
*: statistically significant	

Table-5: Correlation between CRP and BMI

Variables	Leptin and BMI
r value	0.79
p value	<0.01*
*: statistically significant	

Table-6: Correlation between Leptin and BMI

The mean CRP level distribution among the male subjects in the present study was 3.79±0.43. The mean CRP level distribution among the female subjects was 3.73±0.57. The overall mean CRP level distribution among the subjects. was 3.75±0.47 as shown in table 4.

Pearson correlation test was used to find out the correlation between CRP and BMI. A positive correlation was found between CRP and BMI with statistical significance as $p<0.05$ (table 5). Similarly a highly positive correlation was found between Leptin and BMI as $p<0.01$ (table 6).

The above results indicate that serum leptin might be a better biomarker than CRP for predicting nutritional status in ESRD patients on maintenance hemodialysis.

CONCLUSION

Increased serum concentrations of leptin as pro-inflammatory cytokine as well as elevated serum values of CRP and ESR indicate presence of systemic micro inflammation in HD patients. Results of the present study point to possible use of serum leptin concentration as an indicator of nutritional status in HD patients based on observed significant positive correlation between serum leptin concentrations and BMI values. Positive correlation was also found between CRP and BMI, however other studies showed conflicting results. Therefore this requires further investigation and clarification. This study demonstrates the superiority of serum leptin vis-à-vis CRP as a biomarker to assess nutritional status in patients with ESRD on hemodialysis.

DISCUSSION

Malnutrition is an important problem in chronic hemodialysis (HD) patients. Protein energy malnutrition (PEM) is common in renal failure patients and progresses. Mechanisms causing malnutrition in uremia are complex. 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, strongly associated with mortality risk in hemodialysis patients.[12]

Studies reported that 40 – 70% of patients with ESRD were malnourished, with increased mortality. In some observational studies, increased serum leptin concentrations were observed in dialysis patients who lost lean body mass or had hypoalbuminemia with low protein intake. Nonetheless, there are also a number of studies suggesting a paradoxically inverse association between higher serum leptin and improved markers of nutritional status and outcome in chronic kidney disease (CKD). Thus, we aimed to determine the association between serum leptin levels and nutritional status.[13]

Inflammation has generally been agreed to be one of the reasons for anorexia and hypoalbuminemia in hemodialysis patient. Subsequently, Nordfors et al proposed that among the patients with ESRD, leptin gene expression is higher in those who have elevated CRP. Hence it was of interest to examine CRP, the marker of inflammation, and correlate with BMI in hemodialyzed patients.[1]

It has been speculated that hyperleptinemia in ESRD patients may be one of the factors mediating anorexia and malnutrition. However, more recent studies suggest a paradoxically inverse association between higher serum leptin and improved markers of nutritional status, a finding that can be explained by the fact that a higher fat content will secrete more leptin or by the theory of reverse epidemiology in this population. In some observational studies, increased serum leptin concentrations were observed in dialysis patients who lost lean body mass or had hypoalbuminemia with low protein intake. In a cross-sectional study of 28 dialysis patients and 41 healthy control subjects, Johansen et al showed that serum leptin levels were negatively correlated with serum albumin and PCR, suggesting a possible negative role of leptin in nutrition. Stenvinkel et al demonstrated that the increase in serum leptin levels of 36 peritoneal dialysis patients was associated with a decrease in lean body mass. Moreover, Cheung et al studied leptin receptor deficient (db/db) and subtotal nephrectomized mice, and found that those mice had elevated circulating leptin levels and were resistant to the cachexic effects of uremia.[13]

CRP and BMI

Serum CRP level is a sensitive marker of systemic inflammation and a predisposing factor of cardiovascular and atherosclerotic diasease. CRP levels are 8-fold higher in hemodialaysis patients than in healthy controls, being a powerful predictor of all-cause and CVS death, even after a folow up period of 4 years. CRP is present in almost all atherosclerotic plaques, binds to modified low density lipoproteins (LDL) and activates the complement pathway. It has been shown that human CRP can contribute to ishemic tissue damage of heart and brain in experimental rat models. Many studies have shown that elevated CRP levels predict all cause and cardiovascular mortality in patients on hemodyalisis. The 5-year survival rate and the risk of death was significantly poorer in Japanese population of chronic dialysis patients with higher CRP levels. In the study of Krane et al. CVS outcome in dilaysis patients was influenced by CRP levels more than LDL cholesterol levels.[14]

In the current research, mean CRP level distribution among the male subjects in the present study was 3.79±0.43. The mean CRP level distribution among the female subjects was 3.73±0.57. The overall mean CRP level distribution among the subjects was 3.75±0.47. Therefore it can be said that serum leptin levels in this study were higher in patients with CKD on maintenance hemodialysis. Similar to our study, Sanjay et al and reported that the mean CRP levels in HD patients were higher than the upper limit of normal.[2] S. Kaur et al revealed that mean levels of CRP were significantly and markedly higher in patients with CKD compared with that in controls. These findings are in agreement with the hypothesis proposed by Nordfors et al.[1]

In the present study, there was a significant positive correlation between BMI and CRP level. Similar results were reported by Hashimoto et al reported significant positive correlation in such patients. But S. Kaur et al failed to establish any correlation between the CRP levels and BMI in patients with ESRD on maintenance hemodialysis. S. Kaur finding is in close agreement with those reported by Stenvinkel et al and Viikari. This may be attributed to ethnic group differences in physiological norms.[1]

Yildiz et al showed that serum leptin levels were elevated in both hemodialysis and peritoneal dialysis patients, and were significantly correlated with inflammatory markers in this population. However, not all studies consistently show an association between elevated levels of leptin and chronic inflammation, and some studies found that leptin may be a negative acute-phase reactant in patients with CKD. Canivet et al showed that bioincompatible hemodialysis membranes, which activate the complement system and increase cytokine production, are not associated with altered leptin levels when compared with levels observed with biocompatible membranes. Pecoits-Filho et al found that changes in leptin levels negatively correlated with increases in serum CRP, while a positive correlation was observed with levels of other inflammatory markers, such as serum amyloid A, ceruloplasmin, and interleukin-6.[13]

The reason for the discrepancies between the studies may be related to the population recruited, sample size, and design; specifically, serum leptin levels were measured among patients with varying degrees of CKD and different renal replacement therapy.

The limitations of our study included the small sample size and lack of longitudinal data. The findings suggest that leptin and CRP may contribute to malnutrition in HD patients. Further studies are required to ascertain the significance of leptin in relation to nutritional factors in these patients.

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