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Original Article

Physiology Section

Study of the Correlation of Serum Leptin with BMI (A Nutritional Marker) in Patients of End Stage Renal Disease, Who were on Maintenance Haemodialysis

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ABSTRACT

Introduction: Leptin is a small peptide hormone which is produced mainly, but not exclusively by adipocytes. In the general population, it is believed to be an "appetite inhibitor". It is partly cleared by the kidney and is increased in the patients of end-stage renal disease, who are undergoing haemodialysis. There are conflicting reports in the literature about the relationship of serum leptin with the nutritional marker, body mass index (BMI) and studies which are available in the Indian population, which have explored such a relationship, are sparse.

Objective: This study was planned to assess the level of serum leptin and to explore its relationship with body mass index (BMI) in patients of end-stage renal disease (ESRD), who were on maintenance haemodialysis.

Methods: Eighty subjects (forty controls and forty ESRD patients who were on maintenance haemodialysis) were taken for this case-control study. A thorough history was taken and relevant clinical examinations including anthropometric measurements were done. All the subjects were subjected to routine haematological investigations and the evaluation of serum leptin.

Statistical Analysis: The data which was thus collected was subjected to the Student's t-test for studying the significance. A correlation was found between the serum leptin levels and the body mass index by using Pearson's correlation coefficient.

Observations and Result: Patients of ESRD, who were on maintenance haemodialysis, had significantly higher fasting blood sugar, blood urea, serum creatinine and serum leptin levels; and significantly lower haemoglobin levels vis-à-vis the healthy subjects. Serum leptin and body mass index were found to have a positive correlation (r=0.350), with a p value 0.027.

Conclusion: We observed a positive correlation between serum leptin and BMI in patients of end-stage renal disease who were on maintenance haemodialysis, which supported the theory of a reverse epidemiological role of serum leptin in the maintenance of haemodialysis patients.

Key Words: Body Mass Index, Serum Leptin, Renal Failure, Physiology

INTRODUCTION

Chronic kidney disease is a patho-physiological process of more than three months duration with multiple aetiologies, which leads to a gradual and a usually permanent loss of kidney function over time [1]. It is divided into five stages according to its increasing severity. The stage five of chronic kidney disease is also referred to as End Stage Renal Disease and the patients need replacement therapy in the form of haemodialysis, peritoneal dialysis or kidney transplantation [2]. Although there are geographic variations, haemodialysis remains the most common therapeutic modality for chronic kidney disease due to more patient compliance and its availability at peripheral centres [1].

Malnutrition, which is multifactorial in origin, is one of the major hurdles (18-75%) in the long term survival of dialysis patients. The main causes include a restricted diet, metabolic acidosis, gastro-paresis, appetite suppression as a side effect of the drugs, a chronic volume overload, the presence of acute or chronic systemic diseases which cause inflammatory responses and dialysis itself [3]. Therefore, it is recommended to initiate haemodialysis before malnutrition has set in.

Leptin (Greek word 'Leptos' means thin) is a 16 kilodalton protein which was found by Zhang et al in 1994. It is a product of the obese (ob)gene which is secreted primarily from adipocytes [4]. Its gene is located on chromosome 7 and it acts via the JAK **STAT mechanism**. There is a regulatory loop i.e. when the energy stores fall; the declining leptin levels are sensed by the brain and the decreased leptin receptor activation in the hypothalamus causes increased neuropeptide Y production (hyperphagia and obesity) [5].

Some recent studies on maintenance haemodialysis patients have suggested a paradoxically inverse association between higher serum leptin levels and improved markers of nutritional status, a finding that is consistent with the theory of reverse epidemiology [6].

Our study was inspired by the fact that we found controversial results on the correlation between serum leptin and BMI in the literature; and very few studies been done in India, which have explored such a relationship. Thus, our study was planned to determine the level of serum leptin and to find its correlation with body mass index in patients of ESRD who were on maintenance haemodialysis.

MATERIALS AND METHODS

Ours was a case control study which was conducted on eighty subjects (40 cases and 40 controls) who were in the age group of 18-70 years. Patients of end-stage renal disease who were

on maintenance haemodialysis for more than 3 months, who consented to the study, were selected as the cases. Patients who suffered from any acute infection, acute renal failure or any endocrine disorder except diabetes mellitus and who were taking glucocorticoids 8 weeks prior or during the study, were excluded from our study. Forty apparently healthy staff members, with matched ages and body mass index were taken as the controls. This study was approved by the ethical committee of the institution.

Sample Size Calculation

The Kelsey Method for unmatched case-control studies was used to compute the minimum sample size for each BMI category in the cases and the controls, by using the following inputs:

- Two-sided Confidence Level : 95%
- Power (% chance of detecting): 80%
- Ratio of sample size (Controls: Cases): 1
- % of Controls with ESRD on maintenance hemodialysis: 0%
- % of Cases with ESRD on maintenance hemodialysis: 100%

On the basis of the Kelsey Method, we needed a minimum of 4 subjects for each BMI category. To ensure sufficient sample size across the five BMI groups, we selected 40 subjects for both the cases and the control groups.

Investigations

A relevant history was taken and clinical examinations (general and physical, including anthropometry and systemic findings) were carried out, which included:

a. Standing height with bare feet, which was measured accurate to the nearest 0.5cm.
b. Body weight which was recorded with an "Avery" weighing scale, which was accurate to within 50 grams.
c. Body surface area (BSA) in square meter (m^2) which was calculated from the height and weight by using the "Dubois" formula
   $BSA\ (m^2) = Wt\ (kg)^{0.425} \times Ht\ (cm)^{0.725} \times 0.007184$
d. Body Mass Index (BMI) in kg/ m^2: BMI is a reliable indicator for the estimation of body fat, wherein a high value indicates high levels of body fat. It was calculated from total *body mass* (M- i.e. weight in kilograms) and *height* (H-in meters) by using the formula:
   $BMI\ (kg/m^2) = M / (H \times H)$

Routine haematological investigations (haemogram, blood sugar, serum creatinine, urea and lipid profile) and special investigations (serum leptin) were carried out. The DRG Leptin ELISA enzyme immunoassay kit, which was a solid phase enzyme linked immunosorbent assay which was based on the sandwich principle, was used for the quantitative determination of the leptin levels in serum. The average absorbance value (OD) for each set of standards, controls and the patient samples was used for the estimation of the leptin levels in the serum. A standard curve was constructed by plotting the average absorbance value which was obtained from each standard on the vertical (Y) axis against the serum leptin concentration (ng/ml) on the horizontal (X) axis.

STATISTICAL ANALYSIS

The Student's t-test was used for the analysis and a p value of < 0.05 was considered as significant. The correlation between the different parameters was studied by using Pearson's correlation coefficient.

RESULTS

The mean age group was 40.6±15.50 for the cases and it was 41.1±15.8 for the controls. On comparing to the anthropometric data, no significant difference ($p > 0.05$) was observed between the cases and the controls with respect to their age, height, weight and body mass index [Table/Fig-1].

The mean value of various biochemical parameters were calculated and tests of significance were applied. It was observed that the haemoglobin and the random blood sugar levels and the kidney function tests (urea and creatinine) were significant and that the rest (lipid profile and serum electrolytes) were not significant [Table /Fig-2].

SPECIAL INVESTIGATION

The mean value of serum leptin was found to be significantly higher in males as well as in females, in patients of chronic kidney disease who were on maintenance haemodialysis as compared to that in the controls [Table /Fig-3].

[Table /Fig-4] summarizes the mean values ± SD of serum leptin for the various BMI groups across the cases and the controls – it was observed that with an increase in the BMI levels for the cases, the corresponding serum leptin levels also increased. For the two BMI groups (18-20; 20-22 Kg/m^2) for which we had data for both the cases and the controls, we found that the cases had significantly higher levels of serum leptin than the controls.

Serum leptin and BMI showed a statistically significant positive correlation in the cases, with a correlation of 0.351 and a p-value of 0.027 [Table /Fig-5].

DISCUSSION

An attempt is made to determine the levels of serum leptin and to explore their relationship with BMI in patients of ESRD who were on maintenance haemodialysis. In the complex variety of the chronic kidney disease syndrome, malnutrition deserves particular attention. The markers of malnutrition are strongly associated with a poor quality of life [7]. Many causes of malnutrition have been mentioned in the literature; one of them is an increase in the serum leptin levels [3]. Zhangy et al (1994) reported that the hormone, leptin increases in chronic kidney disease and that it may be responsible for the "Anorexia Malnutrition Syndrome" [4].

The mean values ± SD of the serum leptin levels in the present study have been significantly higher in patients of chronic kidney disease who were on maintenance haemodialysis than in the controls. This may be because the kidney is responsible for about 80% of the leptin clearance in healthy individuals. Leptin is cleared from the circulation by the process of glomerular filtration, followed by metabolic degradation in the renal tubules [8].

In patients with normal renal function, there is a net renal intake of 12% of circulating leptin, whereas in patients of chronic kidney disease, there is no renal uptake of leptin [6, 9]. Consequently, the plasma leptin concentrations are found to increase in patients with advanced renal failure, who are undergoing dialysis.

Body Mass Index (BMI) is a simple, accurate and reproducible calculation, based on height and weight. It is considered as one

#	Parameter	Controls	Cases	P-Value
1.	Age(years)	41.10 ± 15.76	40.62±15.55	0.899*
2.	Height(cm)	162.76 ± 6.44	163.34 ± 7.6	0.736*
3.	Weight(kg)	52.9 ± 4.52	52.4 ± 7.65	0.748*
4.	BMI(kg/m^2)	19.96 ± 1.19	19.69 ± 2.60	0.550*

[Table/Fig-1]: Comparison of anthropometric data in two groups of subjects
*Not Significant

#	Parameter	Controls	Cases	P-Value
1.	Hemoglobin (gm%)	12.93 ± 0.58	7.20 ± 1.49	0.000***
2.	Blood Sugar (mg%)	86.67 ± 13.94	99.58 ± 20.52	0.001***
3.	Urea (mg%)	29.10 ± 5.87	150.99± 59.58	0.000***
4.	Creatinine (mg/dl)	0.63 ± 0.29	11.17 ± 5.62	0.000***
5.	Sodium (meq/l)	140.55 ± 3.22	141.07 ± 2.97	0.439*
6.	Potassium (meq/l)	4.02 ± 0.29	4.01 ± 0.27	0.906*
7.	Cholesterol (mg/dl)	198.87 ± 22.64	192.57± 24.64	0.247*
8.	Triglycerides (mg/dl)	124.57 ± 9.28	125.45± 11.47	0.733*
9.	HDL (mg/dl)	54.92 ± 10.18	51.67 ± 7.54	0.075*
10.	LDL (mg/dl)	101.65 ± 15.64	102.25± 14.98	0.855*

[Table/Fig-2]: Mean and standard deviation of Biochemical parameters
*Not Significant; ***Highly Significant

of the markers for the estimation of malnutrition [10]. Studies which are available in the literature, which have looked into the correlation between the serum leptin levels and body mass index in haemodialysed patients of ESRD have controversial results.

The present study further reinforces the direct correlation of serum leptin with BMI in chronic kidney disease patients who were on haemodialysis. This paradoxical inverse association between higher serum leptin levels and an improved nutritional status (increase in BMI) is consistent with the theory of reverse epidemiology [6].

#	Subjects	N	Controls	Cases	P-Value
1	All Subjects	40	0.68±0.55	1.44±0.72	<0.001 ***
2	Males Subjects	20	0.77±0.56	1.17±0.71	<0.001 ***
3	Female Subjects	20	0.59±0.55	1.71±0.64	<0.001 ***

[Table/Fig-3]: Serum Leptin (ng/ml) in males and females across cases and controls
*** Highly Significant

#	BMI	Controls		Cases	
		N	Serum Leptin	N	Serum Leptin
1	< 18 Kg / M^2	4	0.68 ± 0.62	8	1.21 ± 0.62
2	18 – 20 Kg / M^2	10	0.85 ± 0.66	14	1.32 ± 0.89
3	20 – 22 Kg / M^2	16	0.63 ± 0.52	8	1.31 ± 0.46
4	22 – 24 Kg / M^2	5	0.66 ± 0.59	6	1.93 ± 0.59
5	> 24 Kg / M^2	5	0.50 ± 0.49	4	1.83 ± 0.67
Total		40	0.68 ± 0.55	40	1.44 ± 0.72

[Table/Fig-4]: Serum Leptin (ng/ml) for various BMI categories across Cases and Controls

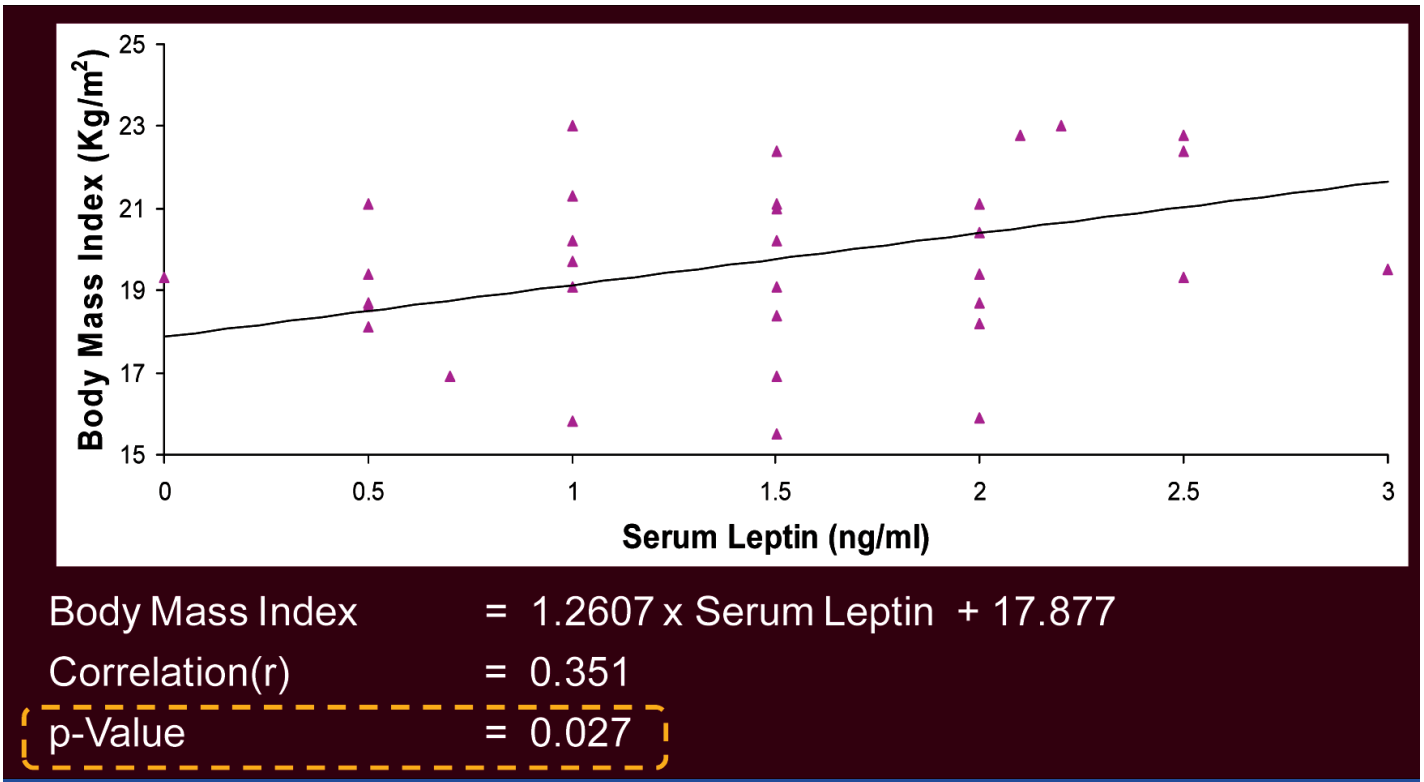
CONCLUSIONS

We observed a positive correlation between serum leptin and BMI in patients of end-stage renal disease who were on maintenance haemodialysis, which supports the theory of a reverse epidemiological role of serum leptin in the maintenance of haemodialysis patients.

SCOPE FOR FURTHER STUDIES

The leptin receptor insensitivity may contribute to an increase in the serum leptin levels and peripheral leptin resistance. Further studies can attempt to assess this impact of leptin receptor insensitivity.

Other pro-inflammatory cytokines such as interleukin 1 (IL 1) and tumour necrosis factor α (TNF α) may also cause inflammation. Further studies can investigate this hypothesis further.



[Table/Fig-5]: Correlation of Serum Leptin with BMI in the Cases (N = 40 Subjects)

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