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Correlation Between Serum Leptin and Insulin Levels: A Case-Control Study

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Abstract: Hypertension (HTN) or high blood pressure (BP) is a chronic disorder in which the pressure exerted on arteries is elevated. Normal BP at rest is below 120/80 mm of Hg. If there is persistent elevation of BP above 140/90 mmHg, it is considered HTN. The prevalence of HTN in obese individuals is twice as high as in the general population. Leptin is an amino acid protein hormone with a molecular weight of around 16kDa. It is a product of the obese gene (ob) from adipocytes. Previous studies revealed the correlation between serum leptin levels and body mass index. The study's novelty is that we assess the correlation between leptin and insulin levels in hypertensive patients. The current study assesses the correlation between hypertensive patients' serum leptin and serum insulin levels. The study's objectives include assessment of age, gender distribution, blood pressure, and comparison of serum leptin and insulin levels among hypertensive and normotensives. This study was conducted among 50 subjects with hypertension(cases) and 50 subjects without hypertension(controls). The study samples were taken from patients who attended the Department of General Medicine outpatient unit at Sri Siddhartha Medical College, Tumkur, Karnataka, India. Results showed that most of the patients were aged 51 to 60 years, and most of the patients were males. There is no significant difference in the gender or mean age between cases and controls. In conclusion, there is a positive correlation between serum insulin and leptin levels among hypertensive and a negative correlation between serum insulin and leptin levels among normotensives. There is a significant difference in the mean serum leptin and insulin levels between hypertensive and normotensives.

Keywords: Case-control study, Correlation, Hypertensive, Insulin, Leptin

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1. INTRODUCTION

Hypertension (HTN) or high blood pressure (BP) is a chronic disorder in which the pressure exerted on arteries is elevated.[1] Normal BP at rest is below 120/80 mm of Hg. If the systolic blood pressure (SBP) is 120-139 mmHg and diastolic blood pressure (DBP) is 80-89mmHg, it is considered pre-hypertension. If there is persistent elevation of BP above 140/90 mmHg, it is considered HTN.[2] HTN continuously strains the heart, causing hypertensive heart disease and coronary artery disease (CAD) if left untreated. It is a major risk factor for aneurysms, stroke, peripheral claudication, and chronic kidney disease. A moderate rise in arterial BP is associated with a shortened life expectancy. Around 50% of hypertensive patients are obese. Obesity causes HTN by activating the sympathetic nervous system, stimulating the renin-angiotensin-aldosterone system, causing modifications in adipose-derived cytokines, causing insulin resistance, and modifying renal function. The prevalence of HTN in obese patients is two times more compared to the general population.[3]Leptin is an amino acid protein hormone with a molecular weight of around 16kDa. It is a product of the obese gene (ob) from adipocytes. Previous studies revealed the correlation between serum leptin levels and body mass index[4-6] Another study revealed that leptin levels are directly proportional to fat mass.[7] Identifying adipocyte-derived leptin brought a novel perspective to the pathophysiological processes of obesity and associated diseases.[8] Hyperleptinemia is more common in obese patients, as leptin is mainly available in the free form among these patients but is present in bound form to a high-affinity protein(leptin receptor) in the blood in lean subjects.[9] This denotes that obesity is a leptin-resistant state.[10] Literature described that leptin regulates appetite and improves energy expenditure by enhancing sympathetic nerve activity in the brown adipose tissue.[11] But, in obesity, leptin loses the capability to stop energy intake and enhance energy expenditure. Hyperinsulinemia or insulin resistance, or both, can be seen in patients with primary or essential HTN.[12]Insulin insensitivity in primary HTN is restricted to nonoxidative metabolism in various peripheral tissues independent of obesity presence.[13]Till now, various studies have been done on lipid profiles in hypertensive patients. However, there are very few studies in developing countries like India on serum leptin and insulin levels among hypertensive patients. The study's novelty is that we assess the correlation between leptin and insulin levels in hypertensive patients. The current study assesses the correlation between hypertensive patients' serum leptin and serum insulin levels. The study's objectives include assessment of age, gender distribution, blood pressure, and comparison of serum leptin and insulin levels among hypertensives and normotensives.

2. MATERIALS AND METHODS

Approval from the institutional ethical committee attached to Sri Siddhartha Medical College, Tumkur, was taken before conducting the study. (Ref: Ethical committee registration number: ECR/137/Inst/KR/2013/RR-19). The approval was expedited review, exempting from taking informed consent, as we are not directly dealing with any patient, and we are just receiving blood samples from the General Medicine Department at our tertiary care centre. The study was conducted in the Department of Biochemistry at a tertiary care centre in south India. We received serum samples from the Department of general medicine and labelled the samples as patients with or without hypertension. This is a comparative study. The duration of the study: 6 months from July 2022 to December 2022. As per STEPS survey[14], the prevalence of hypertension was 15%. Using the sample size formula $N=Z^2PQ/E^2$, the minimum sample size was 43, considering 7% error and 80% confidence intervals. So, we included 50 samples in each group, considering incomplete data for certain samples.

2.1 Eligibility criteria

2.1.1 Inclusion criteria

- Samples of patients aged above 18 years
- Samples of patients of either gender
- Samples of patients diagnosed with hypertension per the Joint National Committee -8 guidelines- for cases.[15]
- Samples of patients with normal blood pressure- for controls

2.1.2 Exclusion criteria

- Samples from patients with severe renal, cardiac, and liver problems that interrupt data collection
- Samples from pregnant and lactating women
- Samples of alcoholics or smokers
- Samples of patients with diabetes mellitus
- Samples of patients with Cushing's syndrome and other endocrinal abnormalities like hypothyroidism leads to obesity.

2.2 Methodology

Informed consent was taken from all patients. A pre-structured proforma was used to collect study parameters. Baseline data, including age, gender, medical history, blood pressure, serum insulin, and leptin levels, were measured. A 5 ml plain venous blood sample was taken from each subject after overnight fasting of 12 hours by venepuncture. The sample was then subjected to centrifugation and processed immediately.

2.3 Exposure measurements

Age, gender, level of education, history of hypertension, and antihypertensive medications were assessed using a predesigned questionnaire. BMI was calculated as weight in kilograms by height in square meters. (Table 4) Serum total cholesterol was measured using the enzymatic method- using oxidase-peroxidase. Total cholesterol levels were assessed using radioimmunoassay (RIA) after collecting a 5 ml plain venous blood sample after overnight fasting of 12 hours by venepuncture. Blood pressure was measured using the digital sphygmomanometer in the resting position. An average of three BP readings was considered. (Table 4)

2.4 *Anthropometric analysis*

2.4.1 Height

Height was measured in centimetres using one vertical board with an attached metric scale. The subject was made to stand barefoot on a flat surface with weight uniformly distributed on both feet, heel together and toes apart, arms by the side, and head positioned so that vision was perpendicular to the body. We connected the head, buttocks, back, and heels to the vertical board. Headboard was brought in contact with the

head to compress hair & reading was recorded to the nearest 0.1 cm.

2.4.2 Weight

Weight was measured in kilograms by making the subject stand on a dial-type weighing machine in the centre of the scale platform facing the recorder, hands at sides, and looking straight ahead.

Body Mass Index was calculated using the formula: Weight in Kg / Height in meter^2

2.5 Biochemical assessments

Estimating serum leptin was done using Sandwich ELISA-Enzyme Immunoassay to determine Leptin in human serum quantitatively. (Table 3).[16] Fasting serum insulin and leptin levels were then assessed. The principle follows a two-step capture or 'sandwich 'type assay. It uses highly specific monoclonal antibodies. The enzymatic reaction is stopped by adding a stopping solution, converting the blue colour to the yellow colour. The absorbance is assessed on a microtiter plate reader at 450nm. Standards are used to plot a standard curve from which the amount of leptin in patient samples and controls can be directly measured. Serum insulin was also tested in a fasting sample using human insulin immunoassay ELISA.[17] (Figure 3) Biochemical investigations like fasting blood samples of 5 ml from all subjects were centrifuged immediately after collection at 3,000×g for 10 min. Serum levels of total cholesterol (TCH) were measured using radioimmunoassay. Serum leptin concentrations were measured using ELISA. Serum glucose is measured using the principle that hexokinase catalyzes glucose phosphorylation to glucose-6- phosphate by ATP. Glucose-6-phosphate dehydrogenase causes the oxidation of glucose-6- phosphate in the presence of NADP to gluconate-6-phosphate. The rate of NADPH formation is directly proportional to glucose concentration. It is measured photometrically.

3. STATISTICAL ANALYSIS

The data collected was entered into an MS Excel 2019, and statistical analysis was carried out using Epi info version 7.2.5 software. Categorical and numerical parameters' association was done using chi-square and student's-test, respectively. A p-value below 0.05 was considered significant. Pearson correlation was used to know the association between numerical parameters. This was done using an online website named staskingdom.com.

4. RESULTS

This study was conducted among 50 subjects with hypertension(cases) and 50 subjects without hypertension(controls). The study samples were taken from patients who attended the Department of General Medicine outpatient unit at Sri Siddhartha Medical College, Tumkur, Karnataka, India.

Table 1: Age distribution of cases and controls

Age distribution	Cases(n=50)	Controls(n=50)	Total
19-30 years	6	5	11
31-40	6	7	13
41-50	10	8	18
51-60	18	14	32
61-70	7	7	14
Above 70	3	9	12

Table 1 shows the age distribution of cases and controls. Most of the patients were aged 51-60 years. The least number of patients were aged below 30 years. 18 patients were aged 41 to 50 years. 14 patients were aged 61-70 years.

4.1 Distribution of gender

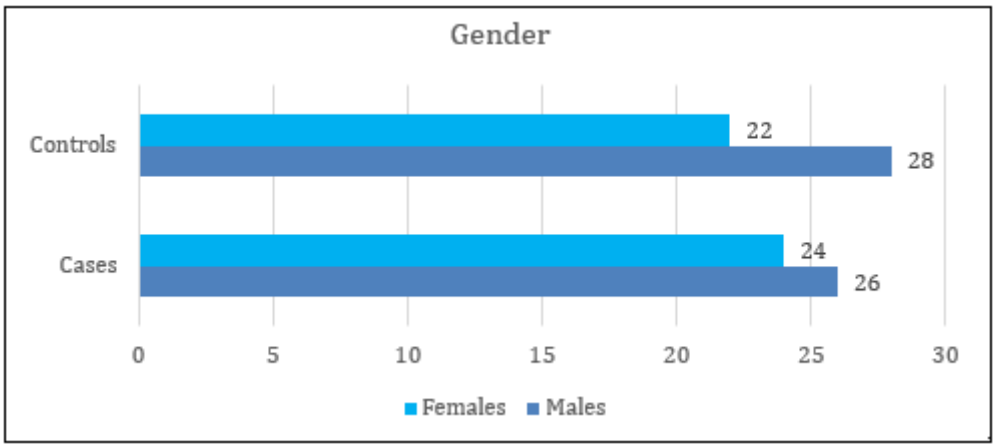

Fig 1: Distribution of gender of cases and controls

Figure 1 shows the gender distribution of patients. 46 patients were females in this study, among 100 patients included. Most of the patients were males. Among 46 females, 24 were cases, and 22 were controls.

4.2 Mean Blood pressure

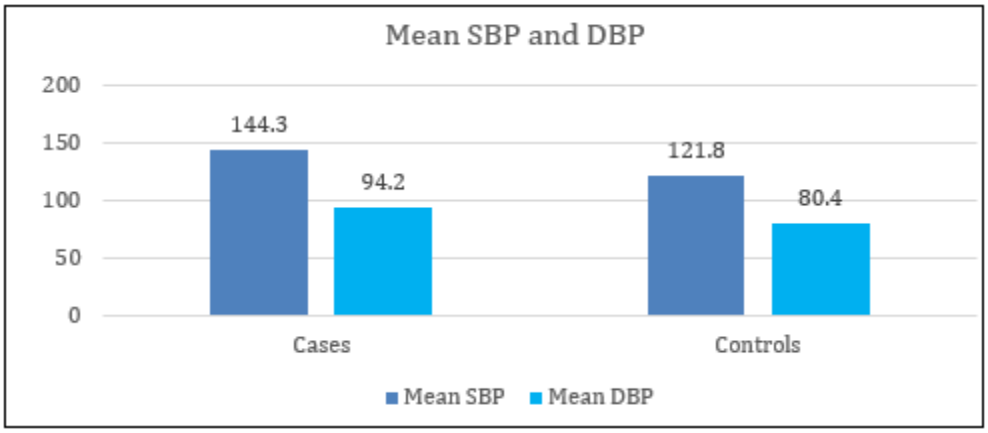

Fig 2: Mean Blood pressure among cases and controls

Figure 2 shows the mean blood pressure between cases and controls. The mean SBP among cases was 144.3 mm of Hg, and the mean DBP among cases was 94.2 mm. The mean SBP among controls was 121.8 mm of Hg, and the mean DBP among controls was 80.4 mm.

4.3 Lipid profile and glucose levels

Table 2: Lipid profile and glucose levels

Lipid profile	Cases(n=50) (HTN patients)	Controls(n=50) (Normotensives)	p-value
Mean serum total cholesterol	248.4±12.1	181.4±11.7 mg/dl	0.0001
Serum triglycerides	201.4±12.9	152.4±18.2 mg/dl	0.0001
Serum LDL levels	152.3±14.3	118.2±12.7	0.0001
Serum HDL	32.4±2.5	36.5±4.2	0.001
Fasting blood glucose (FBG)	141.2±11.1 mg/dl.	102.2±11.9 mg/dl	0.0001
Postprandial blood glucose (PPBG)	290.4±12.9 mg/dl.	161.2±29.8 mg/dl	0.0001
HBA1C (Glycated haemoglobin)	6.4±2.1%	6.1±2.1%	0.03

Table 2 shows biochemical parameters like lipid profile, fasting blood glucose, postprandial glucose, and glycated haemoglobin levels among cases and controls. There is a significant difference in the mean serum total cholesterol, FBG, PPBG, and HbA1c among cases and controls.

4.4 Serum leptin levels among cases and controls

Table 3: Serum leptin levels among cases and controls

Group	Mean levels	p-value
Cases	16.24±2.41	0.001
Controls	12.2±1.75	

Table 3 shows the mean serum leptin levels among all patients. Mean serum leptin levels among cases were 16.24ng/ml, and mean serum leptin levels among controls were 12.2ng/ml. There is a significant difference in the mean serum leptin levels among cases and controls(p=0.0001). Serum leptin levels were higher among cases or hypertensives than controls or normotensives.

4.5 Serum-free insulin levels among cases and controls

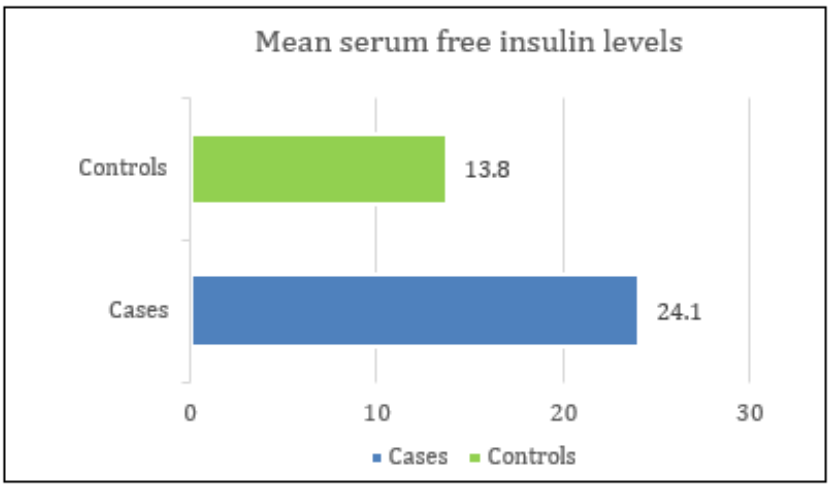

Fig 3: Serum-free insulin levels among cases and controls

Figure 3 shows free serum insulin levels among cases and controls. The mean serum insulin levels among cases were 14.1mcU/ml, and the mean serum-free insulin levels among controls were 13.8mcU/ml(normal). There is a significant difference in the mean serum insulin levels among cases and controls(p=0.001). It was more among cases compared to controls.

4.6 Summary of Clinical characteristics: 100 patients (50 cases and 50 controls)

The following table shows clinical characteristics.

Table 4: Summary of Clinical Characteristics

Clinical features	Cases(n=50) (HTN patients)	Controls(n=50) (Normotensives)	P value
Mean age	55.2±2.1 years	54.6±2.9 years	0.23
Gender Females	24 out of 50	22 out of 50	0.688
Mean BP	144.3±94.2 mm of hg	121.8±80.4 mm of hg	0.0001
Mean BMI	27.7±2.8 Kg/m2	23.1± Kg/m2	0.0001
Mean Blood urea	16.2±2.3	15.1±3.1	0.08
Mean serum creatinine	0.8±0.1	0.89±0.21	0.61
Mean waist circumference	104.2±3.1 cm	92.1±2.1 cm	0.01
Usage of antihypertensives	Yes (100%)	No	NA
Calcium channel blockers	42%	NA	NA
Angiotensin receptor blockers	46%	NA	NA
Others	12%	NA	NA

NA: Not applicable. Table 4 shows mean age, gender, mean blood pressure, mean BMI, mean waist circumference, mean blood urea, mean serum creatinine, and usage of antihypertensives among cases and controls. Since all cases are hypertensive, antihypertensives do not apply to controls or normal subjects.

4.7 Correlation between serum insulin and serum leptin levels among cases

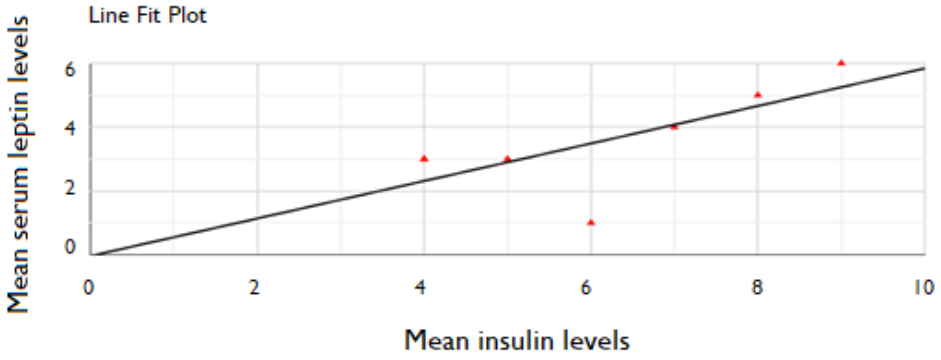

Fig 4: Correlation between serum insulin and leptin levels

Figure 4 shows a significant positive correlation between mean serum insulin and serum leptin levels ($p < .001$). Pearson correlation r= 0.7086. A positive correlation indicates that mean insulin levels as more among patients with more mean serum leptin levels. X-axis: Mean insulin levels, and Y-axis shows mean serum leptin levels.

$$r = \frac{S_{XY}}{S_X S_Y}$$

$$r = \frac{2.2381}{1.9518 * 1.6183} = 0.7086$$

4.8 Correlation between mean serum insulin and serum leptin levels among controls

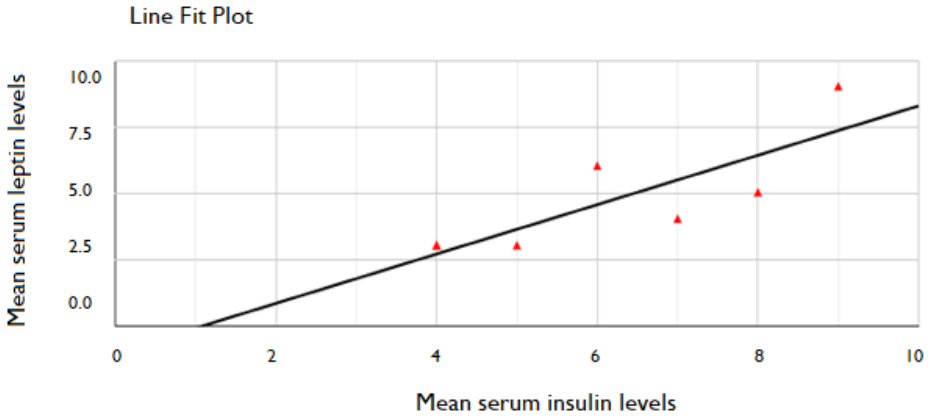

Fig 5 Shows a correlation between mean serum insulin and leptin levels.

Figure 5 shows a line graph- a non-significant, very small negative relationship between X and Y axis and the Pearson correlation ($r = .023$, $p = 0.8207$). This denotes no relation, association, or correlation between serum insulin and leptin levels among normotensive patients(controls). The x-axis shows mean serum insulin levels, and Y axis shows mean serum leptin levels.

$$r = \frac{S_{XY}}{S_X S_Y}$$

$$r = \frac{3.5476}{1.9518 * 2.2147} = \mathbf{0.8207}$$

5. DISCUSSION

Hypertension (HTN) or high blood pressure is a chronic medical disorder in which lateral pressure in the arteries increases. The main mechanism behind HTN is a decrease in arterial compliance. SBP depends on heart and pulse wave velocity. Pulse wave velocity is responsible for the rapid outflow of blood in the diastole, leading to decreased diastolic blood pressure. In 2008, the prevalence of hypertension rate from 5 to 47% in men and 7 to 38% in women in Asia. Incidence is high due to increasing obesity and metabolic syndrome. Thus, it is projected that there will be 29.2% of the global prevalence of hypertension by 2025. [18]By activating its receptor in the hypothalamus, leptin modifies energy expenditure and food intake. It induces proliferation, differentiation, and functional activation of hematopoietic cells. It induces angiogenesis and improves wound healing. Mice with a deficiency in leptin receptors show a decreased incidence of colitis, arthritis, and encephalomyelitis, indicating its role in developing autoimmune diseases.[19-21] We suspect a correlation between serum leptin and insulin levels among HTN patients, so the current study was undertaken. Results showed that most of the patients were aged 51 to 60 years, and most of the patients were males. There is no significant difference in the gender or mean age between cases and controls. There is a positive correlation between serum insulin and leptin levels among hypertensives and a non-significant correlation between serum insulin and leptin levels among normotensives. Leptin increases sympathetic nerve activity among those tissues involved in cardiovascular regulation, like kidneys and blood vessels. Sympatho excitatory effects of leptin enhance arterial pressure.[22] Transgenic mice which overexpress leptin from adipose tissue mass are lean but develop HTN, which is sympathetically mediated, confirming that leptin has a critical link between adiposity, sympathetic activation, and an increase in BP.[23] exogenous leptin administration may not regulate energy homeostasis effectively while maintaining its effects on sympathetic outflow and BP. This "selectivity" in leptin resistance may explain the capability to drive HTN and sympathetic over activity in obese patients as per Mark et al.[24] In the review done by Duanduan[25] et al. authors found a significant relationship between *plasma* leptin levels and blood pressure regulation. This finding was comparable to our study findings. Xun P et al.[26] showed patients in the highest quartile of insulin levels had more incidence of HTN than patients in the lowest quartile. This indicates that patients with HTN have more serum insulin levels. This finding was comparable with current study findings. The study concluded that fasting serum insulin levels in childhood were positively associated with the incidence of

hypertension later in life among men and women reference. Ritika Singla et al.,[27] studied serum insulin levels among HTN patients and found that hypertensive subjects are characterized by more fasting insulin levels (16.77 mcU/ml). This finding was similar to our study results. They have increased BMI and more incidence of dyslipidaemia. There is a non-significant correlation between mean systolic and mean diastolic blood pressure. Zhou et al's review showed abundant clinical and epidemiologic proof demonstrating a close relationship between insulin resistance and HTN. The coexistence of insulin resistance and HTN cause a significant rise in the risk of developing diabetes and cardiovascular disorders.[28]In contrast to our findings that leptin is raised among hypertensive, Von et al.[29] showed that obesity-associated HTN does not depend on leptin's presence. But short-term leptin substitution can raise the BP and heart rate among obese patients with leptin deficiency, implying that leptin is additive in obesity-associated hypertension. Bianchi et al.[30] showed that hypertension patients have high serum insulin levels, similar to our study. Also, insulin and urinary albumin excretion rate have a significant direct correlation. Our study shows a significant positive correlation between serum leptin and insulin levels. Paz et al.[31] also found that leptin and insulin directly regulate each other. Leptin inhibits insulin, and insulin stimulates leptin secretion. Leptin enhances insulin sensitivity by reducing adiposity and lipotoxicity centrally and peripherally. Osegbe et al.[32] found that the prevalence of hyperleptinemia was 92.5% among obese patients. Serum leptin levels positively correlated with insulin resistance, which was especially significant among morbid obese patients. Kumar R et al.[33] did a case-control study in Pakistan in 2020. Cases were obese patients with a BMI of more than. 25 kg/m^2. Serum leptin levels were significantly more among patients with insulin resistance and obesity. The study concluded that obesity was associated with increased serum leptin levels and insulin resistance.

5.1 Limitations

1. Small sample size
2. Single-centre study
3. The duration of hypertension was not assessed
4. A family history of metabolic syndrome was not assessed.

6. CONCLUSION

In conclusion, leptin stimulates sympathetic nerve activity in thermogenic and non-thermogenic tissues through various neurochemical pathways, influencing metabolic and cardiovascular systems. Leptin may have a dual influence on blood pressure control, in which the net effect mainly depends on the balance between pressor action by sympathetic nervous system activation and natriuretic and vasorelaxant effect on renal tubules and vascular endothelium. Long-standing hyperleptinemia may lead to sodium accumulation, leading to blood pressure elevation. Also, hypertension is a part of metabolic syndrome associated with raised insulin levels or insulin resistance. These patients' treatment may be focused on overcoming hemodynamic modifications in HTN like anti natriuresis and sympathetic and renin–angiotensin systems.

7. ACKNOWLEDGMENTS

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8. AUTHORS CONTRIBUTION STATEMENT

Dr. Keshavamurthy planned the entire study and designed the methodology. Dr. Arjun Shekar drafted the manuscript. Dr. Basavaraju monitored the complete process. Dr. Shiva Kumar collected the data. Dr. Vinod Kumar did data analysis using statistical software. All the authors read and approved the final version of the manuscript.

9. CONFLICTS OF INTEREST

Conflicts of interest declared none.

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