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Association of Adiponectin and Leptin Levels in Hypertensive Patients with Various Risk Factors of Metabolic Syndrome: A Cross-Sectional Study

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Abstract

Background: *Hypertension is frequently related to metabolic syndrome, a group of diseases that include obesity, dyslipidemia, and insulin resistance. Adiponectin and leptin are adipocyte-derived hormones that serve important metabolic functions. This study investigates how adiponectin and leptin levels in hypertension individuals correlate with various metabolic syndrome risk factors.*

Materials and Methods: *This cross-sectional study enrolled 330 hypertensive patients aged >20 from the Department of Biochemistry, Teerthanker Mahaveer Medical College & Research Centre Moradabad between 1 Jan 2023 and 30 Dec 2023. Serum levels of adiponectin and leptin were measured using enzyme-linked immunosorbent assay (ELISA). Clinical parameters including body mass index (BMI), waist circumference, blood pressure, and Blood glucose were assessed. ANOVA and Pearson correlation analysis evaluated the association between adiponectin, and leptin with various MetS risk factors and among different stages of hypertension.*

Results: *Of 330 hypertensive patients 240(72.7%) were female and 90(27.2%)were male. Using ANOVA, it was found that Adiponectin and leptin levels showed a significant difference in different stages of hypertension($p<0.05$). Leptin level showed a significant positive correlation with BMI, systolic and diastolic blood pressure in stages 2 and Hypertensive crises($p<0.001$) whereas it showed a positive correlation with BG (<0.05) only in stage 2 of Hypertension. In contrast, Adiponectin levels negatively correlated with BMI, systolic and diastolic blood pressure in stage 1 of hypertension and Hypertensive crises($p<0.05$) whereas they showed a statistically significant negative positive correlation with BG only in Hypertensive cries (<0.001).*

Conclusion: *Our study provides evidence for an inverse association between adiponectin levels and various risk factors of MetS, whereas leptin levels exhibit a positive association with MetS components in hypertensive patients. These findings highlight the potential utility of adiponectin and leptin as biomarkers for assessing MetS risk and guiding therapeutic interventions in hypertensive individuals. Further prospective studies are warranted to elucidate the underlying mechanisms and explore the clinical implications of targeting adiponectin and leptin pathways in managing hypertensive patients with MetS..*

Keywords – *Adiponectin, Insulin resistance, leptin, Metabolic syndrome obesity, type 2 diabetes*

INTRODUCTION

Hypertension, a significant contributor to cardiovascular disease, frequently accompanies metabolic syndrome (MetS), which is a combination of related metabolic disorders linked to a heightened risk of cardiovascular issues [1]. MetS includes central obesity, dyslipidemia, hypertension, and insulin resistance, all of which together lead to an increased

occurrence of cardiovascular events and type 2 diabetes mellitus [1]. Adiponectin and leptin, two adipose tissue-derived hormones, have garnered significant attention for their roles in metabolic regulation and their potential implications in the pathogenesis of both hypertension and MetS [2]. Adipose tissue secretes bioactive chemicals called adipokines, which are essential for controlling metabolism and cardiovascular health. Adiponectin, a hormone that has an inverse relationship with body fat, promotes anti-inflammatory, insulin-sensitizing, and heart-protective effects [3]. Its levels are typically reduced in individuals with obesity and insulin resistance, making it a promising biomarker for assessing metabolic health [3]. Conversely, leptin regulates energy balance and appetite, with elevated levels observed in obesity and associated with insulin resistance [4]. However, beyond their roles, the interplay between adiponectin and leptin in hypertensive patients with diverse MetS risk factors remains to be fully elucidated. They also emerged as pivotal players in the intricate network regulating metabolic homeostasis [4]. Understanding the association between adiponectin, leptin, and specific MetS components in hypertensive individuals is crucial for several reasons. Firstly, elucidating these relationships may uncover novel pathways underlying the development and progression of MetS in hypertensive patients, offering potential targets for therapeutic intervention [5]. Secondly, identifying biomarkers that reflect MetS severity and cardiovascular risk in hypertensive individuals can give information about stratification and guide personalized treatment strategies [6]. Thirdly, insights gained from such investigations can contribute to developing more effective prevention and management strategies tailored to the complex needs of hypertensive patients with MetS [6]. Despite the recognized importance of adiponectin and leptin in metabolic regulation, their precise association with specific MetS components in hypertensive patients remains incompletely understood. [7] Understanding this association is crucial as hypertensive individuals often exhibit a high prevalence of MetS, which exacerbates their cardiovascular risk [7]. In this study, we aim to explore the levels of adiponectin and leptin in hypertensive patients who exhibit various risk factors of metabolic syndrome (MetS). By examining the connections between adiponectin, leptin, and specific components of MetS, such as obesity, dyslipidemia, insulin resistance, and hyperglycemia, this research intends to offer valuable insights into the complex relationship between hormones derived from adipose tissue and metabolic disturbances in the setting of hypertension. This study's findings can aid clinical practice by advancing our understanding of MetS pathophysiology and identifying biomarkers for risk stratification and targeted therapeutic interventions in hypertensive patients.

MATERIAL AND METHODS

Study Design and Participants: This cross-sectional study recruited hypertensive patients aged 20 years [8] and above from Teerthanker Mahaveer Medical College and Research Centre between [1/1/2023] and [30/12/2023]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and patients who were on current use of antihypertensive medication. Participants with secondary hypertension, chronic kidney disease stage 4 or higher, and those on medications affecting adiponectin or leptin levels were excluded [9].

Data Collection: Participants in the study were assessed for various anthropometric measurements, including body mass index (BMI), height, weight, and waist circumference. Waist circumference was measured using a flexible measuring tape. Blood pressure was taken in the morning while the subject was seated, following approximately five minutes of rest, with a calibrated sphygmomanometer or automated BP machine. Fasting blood glucose levels were checked with a calibrated glucometer after an overnight fasting period. Blood samples obtained after fasting were analyzed to determine serum levels of adiponectin and leptin utilizing enzyme-linked immunosorbent assay (ELISA) kits .[10]

Assessment of Metabolic Syndrome Components: According to the NCEP-ATP III criteria for metabolic syndrome, its components include abdominal obesity, measured by waist circumference (greater than 102 cm in men and greater than 88 cm in women), dyslipidemia (elevated triglycerides of 150 mg/dL or more, and low high-density lipoprotein cholesterol levels of less than 40 mg/dL in men and less than 50 mg/dL in women), hypertension (blood pressure readings higher than 130/85 mmHg), and hyperglycemia (fasting glucose levels of 100 mg/dL or greater) were evaluated. [11]

Statistical Analysis: The results were analyzed by using SPSS Software version 28.0. Continuous variables were expressed as mean ± standard deviation (SD). ANOVA (analysis of Variance) was used to analyze parameters across

different stages of hypertension and Pearson correlation analysis assessed the relationships between adiponectin, leptin, and MetS components.

Ethical Considerations: This study was conducted for 1 year after the approval of the College Research Committee (CRC) and Institutional Ethical Committee (IEC). All Patients gave written informed consent and fulfilled inclusion and exclusion criteria.

RESULT

This cross-sectional study included 330 patients diagnosed with hypertension in an age group above 20 years. In 330 patients 240(72.7%)were females and 90(27.2%) were males. These 330 patients were divided into 3 stages based on reference blood pressure values per the American Heart Association guidelines. Out of 330, 80(24.2%) patients were in stage1, 160(48.4%) patients were in stage2 and 90(27.2%) patients were in Hypertensive Crises.

Table 1. Comparison of variables of the study population across different groups of Hypertensive Patients (Mean ±SD) by using ANOVA

Variables	Stage1	Stage 2	Hypertensive Crises	ANOVA P value
BMI	27.1 ± 4.6	33.6 ±5.2	39.1±3.2	<0.001
Waist Circumference	47.9 ±8.8	55.5±7.8	65.6±6.0	<0.05
Systolic Blood Pressure	131.7±2.4	153.6±8.8	194.0±25.8	<0.05
Diastolic Blood Pressure	86.6±2.3	102±4.5	128.5±13.8	<0.05
Blood Glucose	125±8.9	156.8±7.8	189.7±22.8	<0.05
Adiponectin	30.5±8.5	22.1±7.9	16.3±6.01	<0.05
Leptin	17.1±7.8	25.7±7.8	31.2±6.9	<0.05

If the p-value is < 0.05 (significant)

If the p-value is < 0.001 (highly significant)

Table 1 shows a one-way ANOVA test for all the parameters in different stages of Hypertensive patients.

- The levels of BMI showed ($p<0.001$) highly significant difference among different stages of Hypertension.
- The levels of adipokines (adiponectin and leptin), Waist circumference, Blood Glucose, and Systolic and Diastolic Blood pressure($p<0.05$) also showed a significant difference among different stages of Hypertension.

Table 2. Correlation of Components of Metabolic Syndrome with Adipokines (Adiponectin, Leptin) in different stages of Hypertensive patients

Variable	Group	Adiponectin (r-value)	Leptin(r-value)
BMI	Stage1	-0.702*	0.655
	Stage 2	-0.698**	0.685**
	Hypertensive Crises	-0.749**	0.724**
WC	Stage1	-0.765	0.833
	Stage 2	-0.621	0.744
	Hypertensive Crises	-0.685	0.474
SBP	Stage1	-0.788*	0.859
	Stage 2	-0.495	0.533**
	Hypertensive Crises	-0.700**	0.570**
DBP	Stage1	-0.646*	0.657
	Stage 2	-0.633	0.624**
	Hypertensive Crises	-0.629*	0.659**
BG	Stage1	-0.503	0.445
	Stage 2	-0.432	0.454*
	Hypertensive Crises	-0.554**	0.545

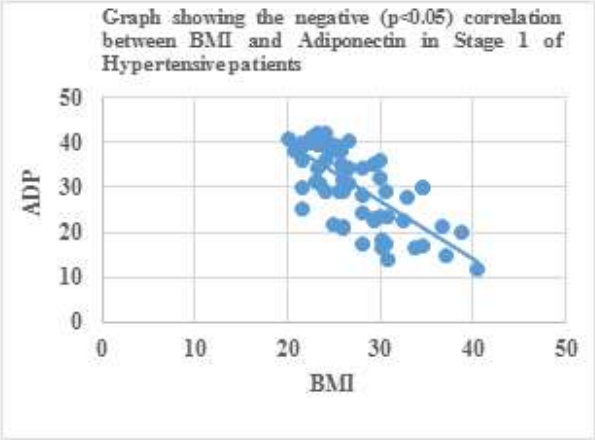
**** Correlation is highly significant at the < 0.001 level**

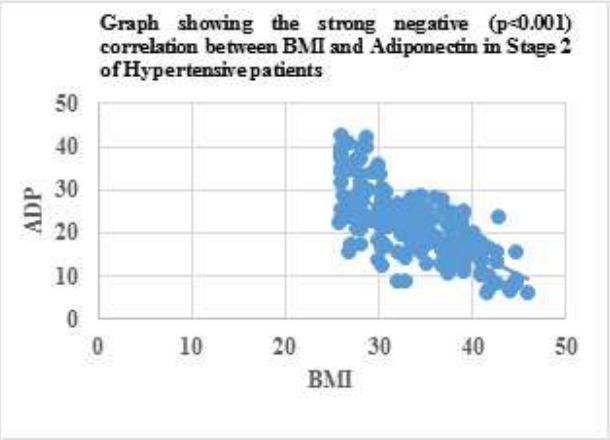
*** Correlation is significant at the <0.05 level**

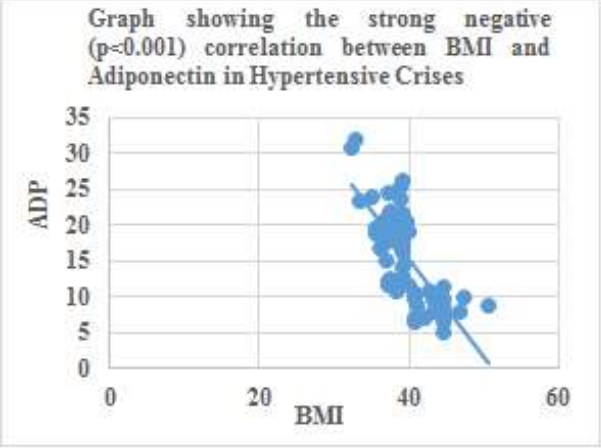
Table 2 shows the correlation of parameters of Adipokines (Adiponectin and leptin) with components of metabolic syndrome in different stages of Hypertensive patients.

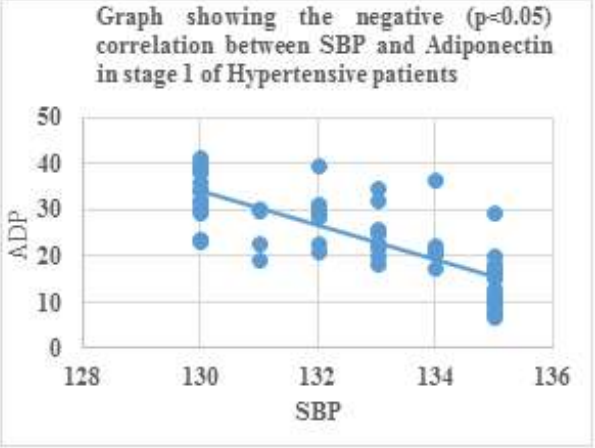
- In Stage 1 of Hypertensive Patients, BMI, SBP, and DBP significantly correlated negatively with Adiponectin ($p<0.05$).
- In Stage 2 of Hypertensive Patients, BMI showed a significant negative correlation with Adiponectin($p<0.001$) whereas BMI, BG, SBP, and DBP show a highly significant positive correlation with leptin($p<0.001$).
- In Hypertensive Crises, BMI, BG, SBP, and DBP showed a significant negative correlation with Adiponectin($p<0.001$) while BMI, SBP, and DBP showed a highly significant positive correlation with leptin ($p<0.001$).

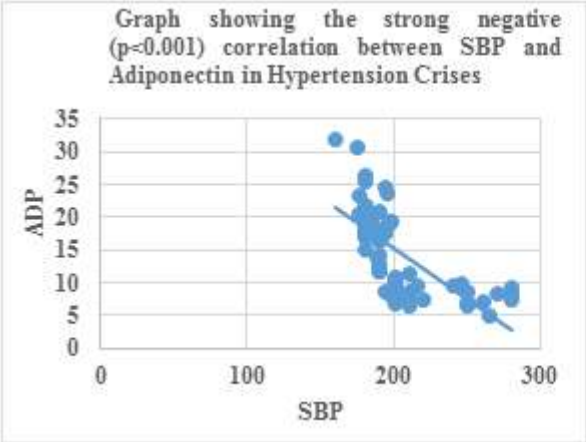
Correlation Graphs of Metabolic Syndrome Components with Adipokines (Adiponectin, Leptin) in Different Stages of Hypertensive Patients

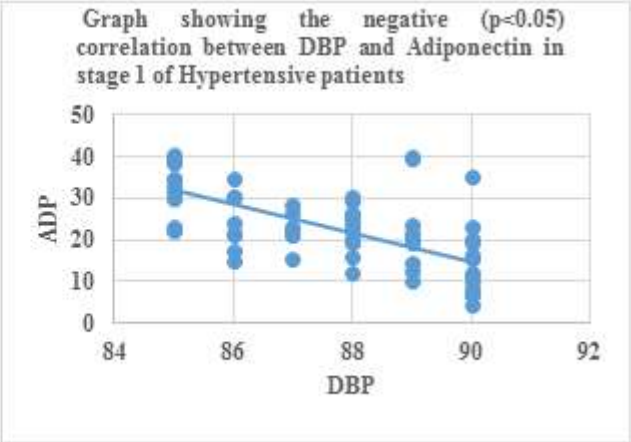


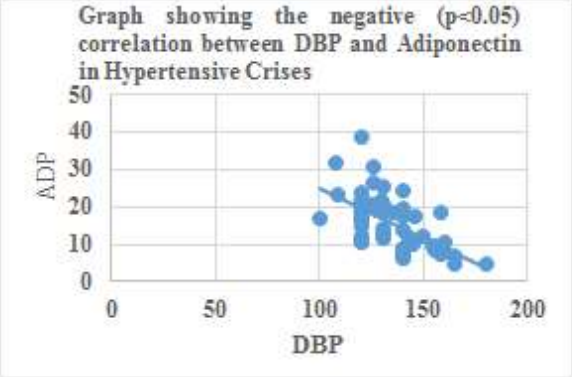


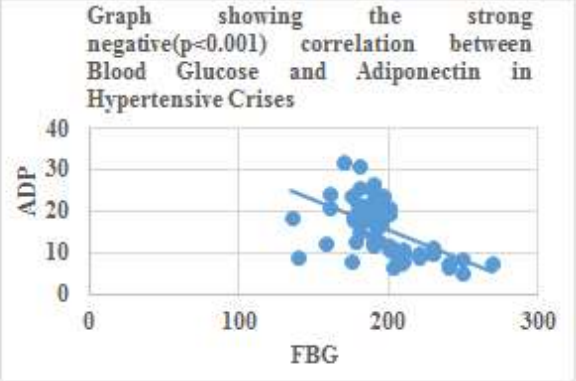


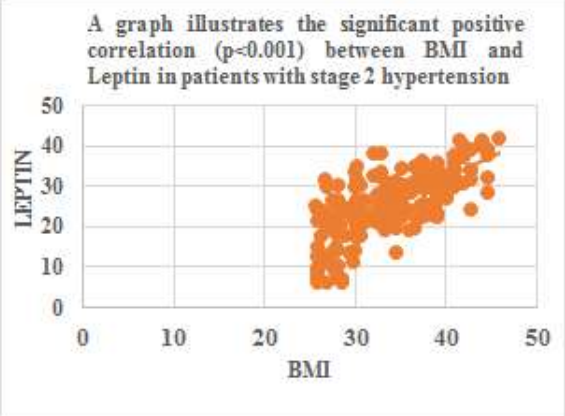


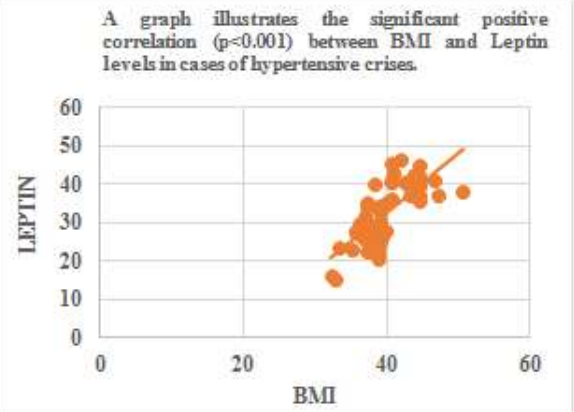

Graph showing the strong negative (p<0.001) correlation between SBP and Adiponectin in Hypertension Crises
ADP
SBP
0
5
10
15
20
25
30
35
0
100
200
300

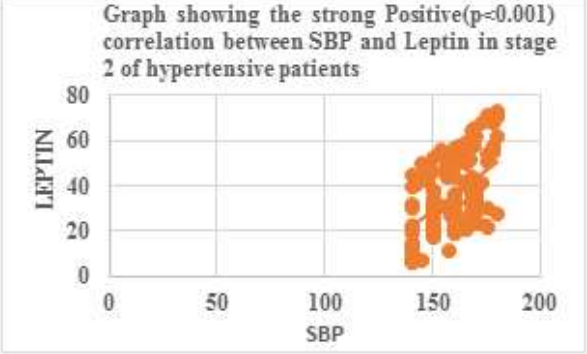

Graph showing the negative (p<0.05) correlation between DBP and Adiponectin in stage 1 of Hypertensive patients
ADP
DBP
0
10
20
30
40
50
84
86
88
90
92

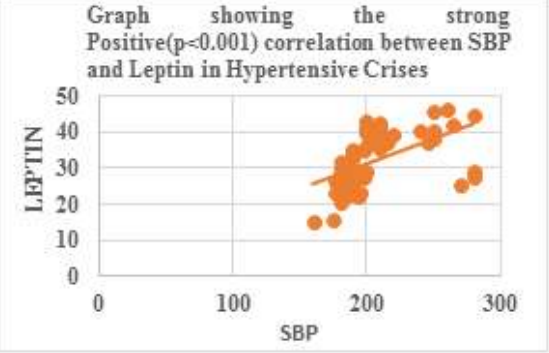

Graph showing the negative (p<0.05) correlation between DBP and Adiponectin in Hypertensive Crises
ADP
DBP
0
10
20
30
40
50
0
50
100
150
200

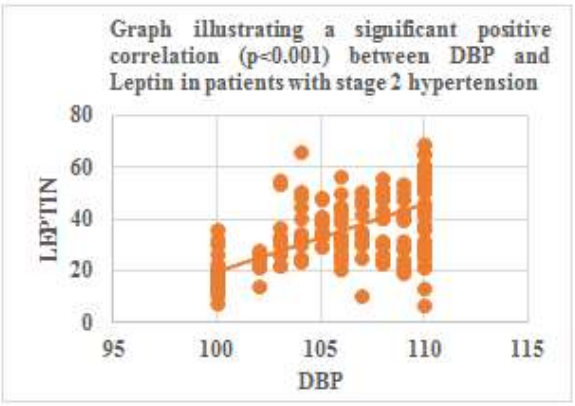

Graph showing the strong negative(p<0.001) correlation between Blood Glucose and Adiponectin in Hypertensive Crises
ADP
FBG
0
10
20
30
40
0
100
200
300

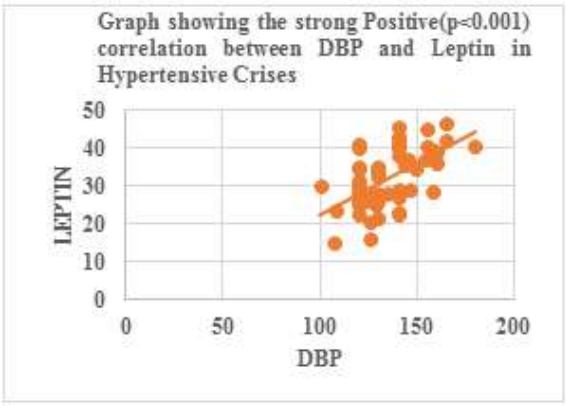

A graph illustrates the significant positive correlation (p<0.001) between BMI and Leptin in patients with stage 2 hypertension
LEPTIN
BMI
0
10
20
30
40
50
0
10
20
30
40
50

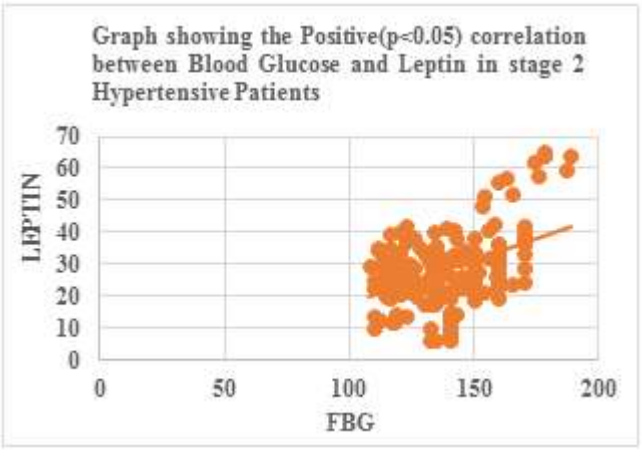

A graph illustrates the significant positive correlation (p<0.001) between BMI and Leptin levels in cases of hypertensive crises.
LEPTIN
BMI
0
10
20
30
40
50
60
0
20
40
60


Graph showing the strong Positive(p<0.001) correlation between SBP and Leptin in stage 2 of hypertensive patients
LEPTIN
SBP
0
20
40
60
80
0
50
100
150
200


Graph showing the strong Positive(p<0.001) correlation between SBP and Leptin in Hypertensive Crises
LEPTIN
SBP
0
10
20
30
40
50
0
100
200
300







DISCUSSION

Hypertension and metabolic syndrome represent major global public health concerns due to their intricate relationships with cardiovascular health. **Metabolic syndrome** is a cluster of risk factors, including **insulin resistance**, **obesity**, **dyslipidemia**, and **hypertension**, that collectively increase the risk of cardiovascular disease. Understanding the underlying mechanisms that link these disorders is crucial for developing effective management and therapeutic strategies [12].

The rising prevalence of obesity, excessive energy intake, urbanization, and sedentary lifestyles has exacerbated the global burden of metabolic syndrome and hypertension. This issue is not limited to underdeveloped countries but is becoming more widespread in urbanized regions, with the prevalence of metabolic syndrome approaching epidemic levels worldwide [13]. Adiponectin and leptin are critical adipokines regulating metabolic and cardiovascular health. Their dysregulation is a central feature of metabolic syndrome and hypertension. Adiponectin's insulin-sensitizing and anti-inflammatory effects counteract the adverse effects of leptin, which promotes insulin resistance, abdominal obesity, and increased blood pressure. Understanding the interactions between these two hormones is vital for the development of therapeutic strategies aimed at preventing and managing hypertension and metabolic syndrome. The findings of this study revealed that the alteration in adiponectin and leptin levels is closely linked to the presence of metabolic syndrome in hypertensive patients [14].

This cross-sectional study included 330 patients aged over 20 years who were diagnosed with hypertension. Among the participants, 240 (72.7%) were female and 90 (27.2%) were male. The patients were categorized into three stages of hypertension according to the American Heart Association guidelines: 80 (24.2%) patients were in Stage 1, 160 (48.4%) were in Stage 2, and 90 (27.2%) were in hypertensive crisis.

Table 1 presents the results of a one-way ANOVA test for each parameter across the different stages of hypertensive patients.

The levels of **SBP and DBP** ($p<0.05$) were all significantly elevated in various stages of hypertension. **Sarfraz ME et.al and Kiro J et al.** found elevated systolic and diastolic blood pressure levels in hypertensive patients [15]. The mechanism behind that is vascular stiffness of the arteries, especially the aorta and large elastic arteries, which results in increased SBP. This happens due to the loss of elastin fibers and increased deposition of collagen in the arterial walls, leading to a reduction in the arteries' ability to expand during systole. The less elastic the arteries are, the 0more pressure is needed to pump blood through them and endothelial dysfunction (impaired functioning of the inner lining of blood vessels) also plays a critical role. It leads to increased vascular resistance and higher SBP and DBP [16].

In all three stages of hypertension, there was a highly significant difference in **BMI** ($p<0.001$). **Mungreiphy NK et.al** [17] showed that the mean of systolic and diastolic BP increased with increasing BMI levels. This study highlighted that higher levels of adiposity, especially visceral fat, are strongly associated with elevated blood pressure. **Landi F et.al** [18] found that **obesity and increased BMI were associated with higher systolic and diastolic blood pressure** in hypertensive patients. This study also noted that individuals with higher BMI levels were more likely to experience **vascular changes** and increased arterial stiffness, further promoting elevated blood pressure. The fluid retention caused by aldosterone not only raises blood pressure but also leads to **higher weight** and **BMI,** contributing to the overall effect of obesity on hypertension. A study by **Wang Y et.al** [19] explored the relationship between BMI and **hypertension in children and adolescents** and found that **overweight and obesity** were significantly associated with an increased risk of developing **high blood pressure**. The mechanism behind this increased visceral fat causes **insulin resistance,** which leads to higher blood sugar levels and increased sympathetic nervous system (SNS) activity. SNS activation causes **vasoconstriction,** raising blood pressure. Additionally, visceral fat releases **pro-inflammatory cytokines** (e.g., tumor necrosis factor-alpha), which contribute to endothelial dysfunction and vascular stiffness, further elevating blood pressure. The increase in abdominal fat leads directly to **higher BMI,** as **visceral fat** is associated with higher overall body mass compared to subcutaneous fat [20].

The level of **Waist circumference** also shows a significant difference in different stages of hypertension($p<0.05$). Some studies are relevant to this result, such as a study by Wei L et.al, which found that **higher waist circumference** was strongly associated with **increased systolic and diastolic blood pressure. Gokhan S. M et.al [21]** emphasized that **visceral fat** (measured indirectly through WC) significantly contributed to **blood pressure elevation,** independent of overall body fat (BMI). **Yusuf S et.al [22] and Tran NTT et.al [23]** found that **increased waist circumference** over time was a **significant predictor** of the **development of hypertension.** The mechanism behind this is abdominal fat storage, particularly visceral fat, driven by insulin resistance and hormonal changes, as well as by sympathetic nervous system activation and its effects on fat mobilization and storage. Chronic inflammation exacerbates metabolic dysfunction and promotes fat accumulation. And Dysregulation of the renin-angiotensin-aldosterone system (RAAS), also influences blood pressure and fat storage [24].

Blood glucose($p<0.05$) shows a significant difference in different stages of hypertension. A study by **Qun Yan et al.[24] and Y Heianza et.al [25]** also found higher blood glucose levels in hypertensive patients. **Zhao S et al.[2]** found that higher levels of **visceral fat** are strongly associated with **impaired glucose tolerance** and **increased fasting glucose levels** in hypertensive patients. The mechanism behind raised blood glucose and hypertension is that hyperinsulinemia may raise blood pressure by boosting sympathetic nervous system activity and increasing renal sodium retention [21, 22]. On the other hand, a chronically overactive sympathetic nervous system may exacerbate insulin resistance, starting a vicious cycle that may eventually result in the development of diabetes and hypertension. Furthermore, decreased peripheral tissue vasodilator response to insulin [21] and enhanced peripheral tissue vasoconstrictor reaction to different vasopressors [22] are linked to insulin resistance. These findings primarily lead to an increase in systolic blood pressure. The intricate pathophysiological process that connects insulin to hypertension remains to be fully understood [21]. Increased carotid body activation from hyperinsulinemia can stimulate the sympathetic nervous system, which can release more adrenaline and norepinephrine, raising peripheral vascular resistance and cardiac output [22]. Elevated catecholamine levels can cause vascular smooth muscle to thicken, which can lead to hypertension [21].

Table 2 shows the correlation coefficients for adiponectin and leptin against various variables (BMI, waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood glucose (BG)) across different stages of Hypertension. In Stage 1 Hypertension, adiponectin negatively correlated with BMI, SBP, and DBP ($p < 0.05$). In Stage 2, adiponectin was negatively correlated with BMI, while leptin showed strong positive correlations with BMI, BG, SBP,

and DBP (p < `0.001). During Hypertensive Crises, adiponectin negatively correlated with BMI, BG, SBP, and DBP, while leptin had strong positive correlations with BMI, SBP, and DBP (p < 0.001).

The level of **Adiponectin** ($p<0.05$) showed a significant difference in different stages of hypertension. Adiponectin levels are significantly lower in hypertensive patients, with studies showing a correlation between reduced adiponectin and hypertension. **IMATOH T et al.** [27] found a decrease in adiponectin in hypertensive patients, while **Kazumi T et al. [28]** reported lower adiponectin levels in young, normotensive Japanese males. **Nigro E et al. [29]** linked visceral fat accumulation to reduced adiponectin and higher hypertension risk. **Lee et al. [30]** found higher adiponectin associated with reduced hypertension risk. Adiponectin negatively correlated with SBP, and DBP ($p<0.05$), in all three stages with the significance becoming stronger in hypertensive crises. These findings are similar to the studies done by **Sharma et al. [31] Koji O et. al,[32], and Takahashi K et al. [33]** Adiponectin, secreted by adipocytes, regulates BP by promoting endothelial function and nitric oxide production. Lower adiponectin levels contribute to endothelial dysfunction, vascular inflammation, and increased vascular resistance, which elevate BP [34]. **In Stage 2,** adiponectin showed a stronger negative correlation with BMI ($p<0.001$) as compared to Stage 1, the findings correlating with the studies done by **Cohen SS et al. [35]** and **Wu O et al.** showing lower adiponectin in individuals with higher BMI and obesity, which worsens hypertension due to chronic inflammation and adiponectin resistance. **Nigro E et al. [29]** found a significant negative correlation between adiponectin and BMI in obese hypertensive individuals. This is because adipocytes predominantly secrete adiponectin and its secretion is reduced in obesity. Lower levels of adiponectin contribute to increased fat storage and metabolic disturbances, including hypertension [29]. **In hypertensive crises,** adiponectin levels show a strong negative correlation with blood glucose apart from BMI, SBP & DBP ($p<0.001$) when compared to stages 1&2. These findings corroborate those of **Jung CH et al.[37]** and **Wu O et al. [36]** Adiponectin improves insulin sensitivity and has anti-inflammatory effects on the vascular endothelium. Low adiponectin exacerbates insulin resistance, endothelial dysfunction, and sympathetic overactivity, contributing to hypertension, glucose intolerance, and metabolic syndrome [38].

Leptin also shows a significant difference in different stages of hypertension($p<0.05$) with higher levels being found in hypertensive patients of **stage 2 and hypertensive crises** than in **stage 1**. These findings correlate with the research performed by **Daghri AL et al [39], and Zhang y et al[40] A** who showed a strong positive correlation in hypertensive crises. Elevated leptin levels in hypertensive crises can be attributed to sympathetic overactivity, vasoconstriction and salt retention all of which increase blood pressure [41]. **Nigro E et al[29]. and Cohen SS et al.[35]** linked leptin resistance in obese hypertensives to elevated blood pressure (BP) and increased sympathetic nervous system (SNS) activity. Visceral fat accumulation, a key factor in hypertension, raises leptin levels, which in turn promotes SNS activation, vasoconstriction, and vascular dysfunction [42]. **In Stage 2 hypertension,** leptin shows a strong positive correlation with blood glucose apart from BMI, SBP and DBP ($p<0.001$). Strong positive correlation with SBP & DBP in Stage 2 hypertensives can be attributed to increased SNS activity and vascular resistance, worsening BP with higher leptin levels as shown by **Landsberg L et al. [43] and Liu Y et al.[44]** Leptin resistance also impairs insulin sensitivity, leading to hyperleptinemia and metabolic syndrome leading to elevated blood glucose, as shown by **Jung CH et al.[45]** Leptin plays a central role in regulating energy balance and glucose metabolism by acting on the hypothalamus and peripheral tissues. This leads to hyperleptinemia and a concomitant increase in blood glucose levels, as leptin continues to promote insulin resistance[45].

CONCLUSION

Our research shows that adiponectin levels negatively correlate with several MetS risk factors, while leptin levels positively correlate with MetS components in hypertensive individuals. These results demonstrate the potential usefulness of leptin and adiponectin as biomarkers for determining the risk of MetS and directing treatment decisions in hypertensive patients. To manage hypertensive patients with MetS, further prospective studies are necessary to clarify the underlying processes and investigate the therapeutic consequences of targeting the adiponectin and leptin pathways.

LIMITATIONS

This study has several limitations, including its cross-sectional design, which precludes causal inference. Additionally, the study population was recruited from a single centre, limiting generalizability. Further longitudinal studies with larger and more diverse populations are warranted to confirm these findings and elucidate the underlying mechanisms.

Randomized controlled trials may be required to establish the cause-and-effect relation.

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