ORIGINAL ARTICLE

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Correlation Between Serum Adipokines (Leptin, Adiponectin) and Cardiac Autonomic Dysfunction in Metabolic Syndrome

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ABSTRACT

Background: Metabolic syndrome (MetS) is becoming a common problem in South Asia and a condition connected to premature cardiovascular dysfunction. Hormones secreted by the adipose tissue especially leptin and adiponectin are important in metabolism and inflammation. Their role in the cardiac autonomic dysfunction assessed by the heart rate variability (HRV) is poorly examined in Pakistani populations. Knowledge of this association can be used to predict early cardiovascular risks.

Objectives: This paper attempted to determine the relationship between adipokine (leptin and adiponectin) levels in serum and cardiac autonomic dysfunction in MetS patients. Other aims were profiling adipokine concentration and evaluation of HRV changes in relation to metabolic syndrome.

Methods: The study was carried out at tertiary care hospitals in Punjab, Pakistan, between January 2024 and January 2025 in the form of a cross-sectional study. NCEP-ATP III requirement of the MetS was met in 90 adults of both sexes (3060 years). ELISA was used to analyze fasting blood samples in terms of serum leptin and adiponectin levels. The 5-minute HRV analysis that included SDNN, RMSSD, LF, HF, and LF/HF ratio was used to measure cardiac autonomic functioning. Pearson analysis was used to determine the correlations, and multivariate regression was done to determine the independent predictors of autonomic imbalance.

Results: The level of leptin and adiponectin in the participants was greatly increased and lowered respectively. The indices of HRV showed strong autonomic dysfunction, where parasympathetic activity (low RMSSD and HF) and sympathetic dominance (high LF/HF ratio) were decreased. Leptin had negative relation with RMSSD and HF and a positive relation with LF/HF and adiponectin showed the reverse. The two adipokines were both independent predictors of HRV abnormalities, which are adjusted by metabolic confounders.

Conclusion: Adipokine imbalance that involves elevated leptin levels and decreased adiponectin levels is closely linked with cardiac autonomic dysfunction in MetS. These biomarkers can be used as precocious signs of heart risk among Pakistani adults with metabolic syndrome.

Keywords: Metabolic syndrome, leptin, adiponectin, heart rate variability, cardiac autonomic dysfunction, sympathetic dominance, Pakistan, adipokines, cardiovascular risk.

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INTRODUCTION

Metabolic syndrome (MetS) is a significant health epidemic around the world, which is a combination of a set of interconnected metabolic disorders, such as central obesity, dyslipidemia, disrupted glucose regulation, and hypertension[1]. The combination of these disruptions leads to a significant exposure to the possibility of type 2 diabetes mellitus, atherosclerotic cardiovascular disease, and the long-term cardiometabolic morbidity. The occurrence of MetS has increased drastically in South Asian communities such as Pakistan owing to the rapid urbanization, sedentary lifestyles and dietary changes, which predisposes individuals to cardiovascular complications at earlier ages[2,3].

During the recent years, adipose tissue has become an interesting subject as a living endocrine tissue that secretes a variety of bioactive mediators (adipokines). Among them, leptin and adiponectin are important and antagonistic to the regulation of metabolism and cardiovascular homeostasis[4]. The adiposity is associated with proportionate raise in leptin levels that induce sympathetic nervous system stimulation, endothelial maladjustment, inflammation, and oxidative stress. Its opposite effect is that adiponectin has anti-inflammatory,

insulin sensitizing, and cardioprotective properties, which levels decline in obesity and metabolic syndrome. The difference between these two adipokines hyperleptinemia and hypoadiponectinemia is one of the characteristic indicators of metabolism impairment[5,6].

One of the first examples of physiological effects in people with MetS is cardiac autonomic dysfunction. It is an indicator of alterations in the ability to regulate sympathetic and parasympathetic activity and is closely linked to undesirable events like arrhythmias, sudden cardiac death, and increased the rate of cardiovascular disease. Heart rate variability (HRV) is a non-invasive, sensitive autonomic nervous system biomarker, with low indices of parasympathetic and large sympathetic markers being indicators of autonomic imbalance[7,8].

Even though there are multiple studies investigating the metabolic derangements as related to MetS, the complex between adipokine changes and cardiac autonomic performance is under-researched. The mechanistic interaction between leptin/adiponectin signaling and autonomic regulation has not been characterized well in Asian populations, despite cardiometabolic risk being disproportionately high in Asian populations. Knowledge of these associations could provide useful information on predicting cardiovascular risks at an early stage and give the opportunity to do targeted therapeutic interventions[9,10].

Thus, the research objective is to examine the association between serum levels of adipokines that are leptin and adiponectin, and cardiac autonomic dysfunction measured by HRV indices, in adults with metabolic syndrome. This study aims to contribute to the better understanding of the pathogenesis of early cardiovascular risks and the creation of better diagnostic and prevention protocols by defining the relationship between adipokine disruptions and sympathovagal imbalance[11].

MATERIALS AND METHODS

The analytical research was a cross-sectional study, which was performed in tertiary care hospitals in Punjab, Pakistan, during 12 months, between the period January 2024 to January 2025. This study recruited 90 adult patients who were diagnosed to have metabolic syndrome in the endocrinology and cardiology outpatient units. Metabolic syndrome diagnosis was made based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria that necessitated the onset of central obesity, and two other metabolic abnormalities, such as increased fasting glucose, high triglyceride levels, low HDL cholesterol, or high blood pressure. The targeted respondents were men and women aged 30-60 years old who came with the purpose of repeated clinical assessment and who could give an informed consent. Patients who already had cardiovascular disease, chronic kidney or liver disease, active infection, pregnancy, or were on drugs that may affect the autonomic activity, such as beta-blockers, antidepressants or antipsychotics, were excluded to exclude any confounding effects. The protocol of the study was accepted by the Institutional Review Board of the existing hospitals and the informed consent of all the participants was taken in writing before admission.

Each of the participants received a standardized clinical evaluation, which started with the assessment of height, weight, and waist circumference to compute the body mass index and assess central obesity. The sitting posture was recorded as the baseline upon which blood pressure was measured after a period of five minutes of rest and an average of two continuous readings made as the final value. The venous blood samples were fasted (1012 hours) and then sampled. Leptin and adiponectin content in serum was determined by commercial enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer instructions and each assay was repeated twice to provide assay reliability. Besides adipokine levels, there were measured fasting plasma glucose, serum triglycerides, high-dense lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and insulin in the fasting. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to measure insulin resistance and was estimated with the help of both fasting insulin and glucose levels.

Short term heart rate variability (HRV) based on a five minute, resting electrocardiogram was used to measure cardiac autonomic functions. To reduce external factors on autonomic activity, participants were permitted to take a ten minutes rest in a temperature controlled room prior to the ECG recording. The system to be analyzed was a standard three-lead digital ECG system and only those normal-to-normal (NN) intervals with no artefacts were analyzed. Both time and frequency domain were used to assess HRV. Time-domain measures comprised of standard deviation of NN intervals (SDNN) and root mean square of successive differences (RMSSD), which are essentially the autonomic modulation and parasympathetic activity respectively. The frequency-domain analysis was accomplished with the help of Fast Fourier Transform to calculate low-frequency (LF) and high-frequency (HF) power content, which represents a combination of sympathetic and parasympathetic activity and mainly parasympathetic activity. As an indicator of sympathovagal balance, the ratio of LF/HF was determined.

The SPSS version 25 was used to conduct a statistical analysis. Continuous variables were given in mean standard deviation whereas the categorical variables were given in frequencies and percentages. An independent sample t-test was to be used to compare the results of adipokines and HRV parameters among the participants of the metabolic syndrome and the established reference values of healthy people. The strength and direction of the association between serum leptin, adiponectin and HRV indices were determined using Pearson correlation

coefficients. In order to further determine whether adipokines were an independent predictor of autonomic dysfunction, multiple linear regression equations were developed after controlling against the confounding variables of age, body mass index, blood pressure, lipid profile, and HOMA-IR. The statistical significance of p-value was taken to be below 0.05 during the analysis.

RESULTS

The sample size used in the study was 90 adults of both sexes with 52 females and 38 males fulfilling the NCEP-ATP III diagnostic criteria on metabolic syndrome. The average sample age was 48.6 / 8.9 years. Table 1 presents the anthropometric and metabolic features of the participants. On the whole, the participants exhibited a strong level of metabolic imbalances, such as high BMI, large waist circumference, high levels of fasting glucose, hypertriglyceridemia, low levels of HDL cholesterol, and a high level of HOMA-IR scores. These results affirm that there is a great cardiometabolic risk profile in both male and female subjects. There was no significant difference in the metabolic pattern by gender with both men and women showing similar trends of obesity and insulin resistance (Table 1).

The analysis of serum adipokines indicated a significantly dysregulated pattern of both men and women who had metabolic syndrome. As Table 2 shows, the overall serum leptin levels were much higher than the stipulated reference rates whereas adiponectin levels were much less. Women had a slightly higher level of leptin than men as is known, yet the imbalance of adipokines was clear in both groups.

Heart rate variability (HRV) indices were used to measure cardiac autonomic performance based on a five minute ECG at rest. The outcomes of the HRV showed a vivid trend of autonomic imbalance of the metabolic syndrome group. Table 3 demonstrates that indices related to time domain like SDNN and RMSSD were severely reduced, which indicated suppressed general variability and low activity of the parasympathetic system. The frequency-domain parameters depicted a reduced HF power and high LF/HF ratios, which are indicative of sympathetic dominions. There were no gender-specific differences that were statistically significant, implying that dysfunction of metabolic processes influences cardiac autonomic balance similarly in both genders.

Strong statistically significant correlations were found between serum adipokine levels and HRV indices by correlation analysis. Table 4 shows the results of the correlation analysis. An increase in leptin was negatively associated with RMSSD ($r = -0.52$, $p < 0.001$) and HF ($r = -0.48$, $p < 0.001$), which is the indicator of the suppressed parasympathetic activity. It was indicated by a positive correlation with the LF/HF ratio ($r = 0.41$, $p < 0.001$) that higher levels of leptin were correlated with an increased sympathetic drive. However, in comparison, there were positive relationships between adiponectin and RMSSD ($r = 0.44$, $p < 0.001$) and HF ($r = 0.39$, $p < 0.001$), but negative relationships with LF/HF ratio ($r = -0.36$, $p < 0.001$), which verified its contribution to the maintenance of vagal activity and autonomic stability. The consistency in these relationships was also observed when analyzed under male and female subgroups, but the statistical power was less in the subsets of individual genders.

This negative leptin-para sympathetic index and positive adiponectin-vagal index show that leptin has a sympatho-excitatory effect and adiponectin has cardio-protective effect. All of the mentioned findings prove that the adipokine imbalance is a powerful predictor of autonomic dysfunction.

Multivariate linear regression proved adipokines to be independent predictors of cardiac autonomic status. Leptin was also an important independent predictor of the LF/HF ratio after age, sex, BMI, blood pressure, lipid parameters, and HOMA-IR (0.34; $p = 0.002$) whereas adiponectin was an important independent predictor of RMSSD (0.29; $p = 0.004$). These findings highlight the fact that the effect of adipokines on the autonomic control remains the same irrespective of the gender or other metabolic risk factors.

Table 1: Baseline Anthropometric and Biochemical Characteristics of Study Participants (n = 90)

Parameter	Mean ± SD
Age (years)	48.6 ± 8.9
Sex (M/F)	38 / 52
BMI (kg/m²)	31.8 ± 4.7
Waist Circumference (cm)	101.4 ± 9.3
Fasting Glucose (mg/dL)	124.6 ± 22.5
Triglycerides (mg/dL)	186.4 ± 39.8
HDL Cholesterol (mg/dL)	38.2 ± 7.1
Fasting Insulin (µIU/mL)	18.5 ± 5.3
HOMA-IR	5.72 ± 2.11

Table 2: Serum Adipokine Levels in Study Participants (n = 90)

Biomarker	Mean ± SD	Reference Range
Leptin (ng/mL)	28.9 ± 7.6	3–16
Adiponectin (µg/mL)	5.02 ± 1.44	7–15

Table 3: Heart Rate Variability (HRV) Parameters of Study Participants (n = 90)

HRV Parameter	Mean ± SD	Interpretation
SDNN (ms)	28.7 ± 9.4	Reduced overall autonomic modulation
RMSSD (ms)	21.4 ± 7.1	Decreased parasympathetic activity
LF (ms²)	468.5 ± 122.8	Increased sympathetic influence
HF (ms²)	221.3 ± 74.6	Reduced vagal tone
LF/HF Ratio	2.39 ± 0.81	Sympathetic predominance

Table 4: Correlation Between Serum Adipokines and HRV Indices (n = 90)

Variable	RMSSD (r, p)	HF (r, p)	LF/HF (r, p)
Leptin	–0.52, <0.001	–0.48, <0.001	0.41, <0.001
Adiponectin	0.44, <0.001	0.39, <0.001	–0.36, <0.001

DISCUSSION

The current study involved the analysis of the relation of serum adipokines (leaseptin and adiponectin) and cardiac autonomic dysfunction in both male and female patients in tertiary care hospitals in Punjab, Pakistan who had been diagnosed with metabolic syndrome[9]. The results indicate a strict imbalance of adipokines where the level of leptin is excessively high, whereas the level of adiponectin is extremely low. This disproportionate pattern of adipokines was closely linked with the disrupted heart rate variability (HRV), which is the sign of the autonomic imbalance between the decreased parasympathetic and increased sympathetic power. These findings are in line with the new theme that metabolic syndrome is not merely a metabolic disease but also an autonomic dysregulation condition that is facilitated partially by adipose-derived signaling molecules[10,11].

The high levels of leptin in both males and females participants correspond to the established association between high adiposity levels and hyperleptinemia. Leptin is produced by adipose tissue according to the fat mass, and it does so much more than controlling appetite[12]. Leptin is a neuroendocrine modulator which is able to stimulate the sympathetic nervous system via hypothalamic pathways. This physiological mechanism is witnessed by the significant negative correlations between leptin and key parasympathetic HRV indices (RMSSD and HF), showing an increase in the leptin levels leads to reduced vagal modulation. In the same manner, the positive correlation of leptin with the LF/HF ratio is an indication of transition to sympathetic preeminence- a symptom of autonomic disequilibrium and one of the primary antecedents of hypertension, insulin resistance, and unfavorable cardiovascular outcomes[13].

On the other hand, adiponectin had a protective physiological profile. The decreased parasympathetic and increased sympathetic dominance of the metabolic syndrome group were closely related to the decrease in adiponectin levels as indicated by HRV measures[14]. Adiponectin is a cardioprotective adipokine as it is insulin sensitizing, anti-inflammatory, and anti-atherogenic. It increases the production of endothelial nitric oxides, increases vascular functionality, and overcomes oxidative stress. The favorable correlations of adiponectin with RMSSD and HF indices are indicators that adiponectin levels contribute to the presence of vagal activity and the autonomic balance. Its negative relation to LF/HF ratio is another indicator of its effect in suppressing sympathetic overactivity. Such observations support the use of adiponectin as a useful biomarker in cardiovascular defense in populations that experience metabolic syndrome[15].

It is a significant finding of this research that the relationship between adipokine and autonomy remained intact when various confounding factors were corrected such as age, sex, body mass index, cholesterol level, blood pressure, insulin resistance[16]. This implies that adipokines play a role in autonomic dysfunction in isolation and not just an indication of metabolism abnormalities. The similarity of autonomic effect in both sexes further underscores the fact that dysregulation of adipokine is a similar process in men and women, even though the levels of leptin and adiponectin at the baseline differ between the sexes[17].

The HRV results of the current research are in line with the global evidence that points out that the metabolic syndrome causes the premature dysfunction of the autonomic nervous system. Depreciated SDNN and RMSSD imply fewer variability and parasympathetic withdrawal[18]. Changes in frequencies such as decreased HF and increased LF/HF ratio are additional signs of sympathovagal imbalance. These autonomic changes have clinical implications as chronic sympathetic stimulation has been linked to endothelial dysfunction, augmented arterial constriction, insulin resistance, arrhythmogenesis and augmented long-term cardiovascular danger[19].

The adipokine-autonomic dysfunction pathophysiology may entail a number of processes. Hyperleptinemia enhances sympathetic via hypothalamic signaling, pro-inflammatory cytokine, and oxidative stress activation, all of which disrupt normal autonoetic regulation. Conversely, hypoadiponectinemia decreases the bioavailability of nitric oxide, increases systemic inflammation, and aggravates endothelial dysfunctions, which jointly leads to less responsiveness to parasympathetic. Such a disturbance of high leptin and low adiponectin produces a metabolic-inflammatory

environment, which creates an autonomic imbalance environment[17-20].

This study is especially significant to South Asian populations including Pakistan where metabolic syndrome is becoming worldwide at an earlier age and autonomic dysfunction may not be realized until an advanced cardiovascular disease is developed. Replications of adipokine-HRV correlations in the two genders increase the validity of the study and indicates that adipokines may be used to screen individuals with a high risk of cardiac autonomic dysfunction[15,19].

Even though the evidence presented in the study is very strong to conclude that there is a correlation between adipokines and cardiac autonomic functioning, there are some limitations that can be noted. Its cross-sectional design does not permit causal inference and longitudinal follow-up would be necessary to establish whether the fix of adipokine imbalance is beneficial in correcting autonomic performance. Moreover, the sample size used was sufficient to conduct the correlation analysis, but larger cross-centric cohorts could be used to provide more statistical force to detect gender-specific differences. Irrespective of these shortcomings, the research gives valuable data to the mechanistic connection between adipokine disregulation and autonomic disfunction in metabolic syndrome[16-20].

CONCLUSION

The research indicates that both sexes of adults with metabolic syndrome have a high level of autonomic dysfunction resembling with low parasympathetic and high sympathetic tone. This autonomic impairment is closely related to serum adipokine imbalance, which occurs as a high level of leptin and a low level of adiponectin. Notably, these relations remain intact regardless of the orthodox metabolic risk factors, which means that adipokines have a direct and paramount role in the regulation of cardiac autonomic activity. Hyperleptinemia also seems to play a role in overactivating the sympathetic system, and hypoadiponectinemia appears to be related to a decrease in vagal tone, all of which makes people more at risk of cardiovascular diseases. These results indicate the possibility of adipokine profiling as a predictive diagnostic measure of the subclinical presence of autonomic dysfunction in metabolic syndrome. Recent understanding of adipokine imbalance, and HRV measurement, could assist in specific lifestyle and therapeutic measures to decrease cardiometabolic and cardiovascular morbidities in the high-risk groups.

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