DOI:https://doi.org/10.53350/pjmhs20231710200

ORIGINAL ARTICLE

Integrated Evaluation of Adipokines, Cardiac Biomarkers, and Autonomic Nervous System Activity in Patients with Metabolic Syndrome: A Cross-Sectional Clinical Study

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ABSTRACT

Background: Metabolic syndrome (MetS) is a cluster of interrelated cardiometabolic risk factors that significantly increase the likelihood of cardiovascular disease. Recent evidence highlights the roles of adipokines, cardiac biomarkers, and autonomic dysfunction in the pathophysiology of MetS.

Objective: To evaluate the integrated relationship between serum adipokines, cardiac biomarkers, and autonomic nervous system function in patients with MetS.

Methodology: This cross-sectional study included 100 patients diagnosed with MetS as per IDF criteria. Serum levels of adipokines (leptin, adiponectin, resistin), cardiac biomarkers (troponin I, NT-proBNP, CK-MB), and heart rate variability (HRV) parameters were assessed. Statistical correlations between biochemical parameters and autonomic function indices were analyzed.

Results: Elevated leptin and resisting levels, along with reduced adiponectin, were significantly associated with abnormal cardiac biomarkers and impaired HRV indices ($p < 0.05$). A strong inverse correlation was observed between adiponectin and NT-proBNP ($r = -0.42$), while leptin positively correlated with reduced HRV time-domain measures.

Conclusion: This study suggests a strong interplay between adipokine dysregulation, cardiac stress, and autonomic dysfunction in MetS patients. Integrated biomarker evaluation may offer a promising approach for early cardiovascular risk stratification in this high-risk population.

Keywords: Metabolic Syndrome, Adipokines, Cardiac Biomarkers, Heart Rate Variability, Autonomic Dysfunction, Cross-Sectional Study.

INTRODUCTION

Metabolic syndrome (MetS) has emerged as one of the most pressing non-communicable health challenges of the 21st century, representing a global epidemic with profound implications for cardiovascular and metabolic health[1]. Characterized by a constellation of interrelated clinical and biochemical abnormalities including central obesity, insulin resistance, hyperglycemia, dyslipidemia, and elevated blood pressure MetS predisposes individuals to an increased risk of type 2 diabetes mellitus, ischemic heart disease, stroke, and premature mortality. According to global estimates, approximately 20–25% of the adult population meets the diagnostic criteria for MetS, with this prevalence steadily increasing due to rapid urbanization, sedentary lifestyles, and poor dietary patterns [2].

In Pakistan, the burden of MetS is of particular concern. Various cross-sectional studies have reported prevalence rates ranging from 18% to over 40%, depending on the population studied and the diagnostic criteria applied [3]. Urban communities, in particular, demonstrate a higher incidence of metabolic abnormalities, largely attributed to physical inactivity, high-calorie diets, poor public health awareness, and limited access to preventative care. Alarmingly, even in rural areas, the transition towards Westernized lifestyles has led to a surge in obesity and metabolic disorders. These trends threaten to overwhelm the country's already fragile healthcare system, making early identification and risk stratification of MetS patients a critical public health priority[4, 5].

Despite the well-documented clinical features of MetS, the underlying molecular and physiological mechanisms that link its metabolic components to long-term cardiovascular complications remain inadequately defined. Traditional risk models often fail to detect subclinical disease in time to initiate effective interventions[6].

Received on 25-06-2023
Accepted on 10-09-2023

A growing body of evidence suggests that this syndrome is more than a sum of its parts it is underpinned by complex interactions among adipose tissue-derived signaling molecules, myocardial stress pathways, and autonomic nervous system (ANS) imbalances that cumulatively drive adverse cardiac outcomes[7].

Adipose tissue, once thought to be a passive energy depot, is now recognized as a dynamic endocrine organ with systemic metabolic and inflammatory influence. It secretes bioactive peptides known as adipokines, including leptin, adiponectin, and resistin, which regulate insulin sensitivity, inflammatory responses, lipid metabolism, vascular homeostasis, and myocardial function[8]. An imbalance in these adipokines characterized by elevated leptin and resistin levels and reduced adiponectin is frequently observed in individuals with MetS and has been linked to endothelial dysfunction, oxidative stress, and increased atherothrombotic risk. These alterations not only perpetuate metabolic dysfunction but also contribute to the early development of cardiovascular pathology[9].

Concurrently, cardiac-specific biomarkers such as cardiac troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), and creatine kinase-MB (CK-MB) have demonstrated value in detecting subclinical myocardial injury and ventricular strain in patients who are otherwise asymptomatic[10]. Elevated levels of these biomarkers in individuals with MetS may serve as early indicators of silent myocardial remodeling or low-grade ischemic stress, which, if undetected, can progress to overt heart failure or acute coronary syndromes[11].

Equally important is the role of the autonomic nervous system, which maintains cardiovascular homeostasis through a delicate balance between sympathetic and parasympathetic activity. Heart rate variability (HRV) analysis a non-invasive measure of ANS function has emerged as a powerful tool in assessing autonomic tone[12]. In MetS patients, HRV parameters often reveal diminished parasympathetic activity, increased sympathetic output, and reduced overall autonomic adaptability. This autonomic imbalance has been implicated in the

pathogenesis of hypertension, arrhythmias, and sudden cardiac death. The presence of such dysregulation, even in the absence of clinical cardiovascular disease, reflects a heightened state of neurocardiac vulnerability that may go unrecognized by routine clinical assessments[13].

While the individual contributions of adipokines, cardiac biomarkers, and HRV indices to MetS pathophysiology have been previously described, the literature lacks integrative studies that concurrently evaluate these three domains in a unified framework[14]. In the context of Pakistan where cardiovascular disease represents a leading cause of mortality and where resource constraints limit the feasibility of advanced imaging or invasive diagnostics biomarker-based approaches may provide a cost-effective and scalable solution for early detection and preventive stratification[15].

Therefore, this study was designed to investigate the integrated relationship between serum adipokine profiles, cardiac-specific biomarkers, and autonomic nervous system function in patients diagnosed with metabolic syndrome[16]. By adopting a cross-sectional, multidimensional approach in a Pakistani clinical setting, current study aimed to elucidate the interplay between metabolic and neurocardiac factors, identify early markers of cardiovascular compromise, and establish a foundation for population-specific screening strategies. Ultimately, such integrative assessments may help bridge the gap between molecular research and clinical practice, enabling more personalized, anticipatory, and preventive care for individuals at high risk of cardiometabolic disease[17].

MATERIALS AND METHODS

Study Design and Setting: This hospital-based, cross-sectional observational study was conducted over a 12-month period, from June 2022 to May 2023, at two tertiary care teaching hospitals in Pakistan: the Department of Internal Medicine and Cardiology at Sandeman Provincial Hospital, Quetta, and Liaquat National Hospital, Karachi. The study received ethical approval from the Institutional Review Boards of both participating centers. All enrolled individuals provided written informed consent before inclusion in the study. The study adhered to the ethical standards set forth in the Declaration of Helsinki and complied with relevant national research regulations.

Eligibility Criteria: Participants were eligible for inclusion if they were adults aged between 30 and 65 years, of either gender, and had a confirmed diagnosis of metabolic syndrome according to the International Diabetes Federation (IDF) 2005 criteria. Central obesity was a prerequisite for diagnosis and was defined by a waist circumference of ≥90 cm in men and ≥80 cm in women, reflecting South Asian-specific cutoffs. In addition to central obesity, at least two of the following four abnormalities were required: fasting plasma glucose ≥100 mg/dL or known type 2 diabetes mellitus; serum triglycerides ≥150 mg/dL or receiving treatment for hypertriglyceridemia; HDL-cholesterol <40 mg/dL in men or <50 mg/dL in women; and systolic/diastolic blood pressure ≥130/85 mmHg or ongoing antihypertensive therapy.

Patients were excluded if they had a history of clinically diagnosed cardiovascular disease, including myocardial infarction, heart failure, or documented ischemic heart disease. Additional exclusion criteria included chronic kidney disease stage III or above, active malignancy, autoimmune disorders, or current use of medications that could affect autonomic nervous system activity, such as beta-blockers, calcium channel blockers, or anticholinergic drugs. These criteria were applied to eliminate potential confounding effects on heart rate variability and cardiac biomarker profiles.

Demographic and Clinical Data Collection: Demographic and clinical data were obtained using a pre-designed structured questionnaire. Recorded variables included age, gender, body mass index (BMI), waist circumference, smoking status, and physical activity level, which was assessed using a validated physical activity questionnaire. Blood pressure was measured in the right arm using a calibrated mercury sphygmomanometer after the patient had been seated at rest for five minutes. Anthropometric measurements such as weight, height, and waist circumference were performed using standard World Health Organization (WHO) protocols. Fasting blood glucose and lipid profiles were analyzed in the hospital's certified clinical laboratories using automated biochemical analyzers.

Biochemical Analysis: Fasting venous blood samples were collected from each participant under aseptic conditions after a minimum 10-hour overnight fast. Blood samples were centrifuged at 3000 rpm for 10 minutes to separate serum, which was subsequently stored at −80°C until analysis. Serum concentrations of the adipokines leptin, adiponectin, and resistin were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's protocols and quality control procedures. Similarly, cardiac biomarkers, including troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), and creatine kinase-MB (CK-MB), were quantified using standardized ELISA techniques. All measurements were performed in duplicate to ensure reliability, and assay precision was maintained using internal calibrators and controls.

Autonomic Function Testing: Heart rate variability (HRV) was used as a non-invasive method to assess autonomic nervous system activity. A five-minute resting electrocardiogram (ECG) recording was obtained using a validated portable digital ECG device in a quiet, temperature-controlled environment. All measurements were taken in the morning between 8:00 AM and 10:00 AM, with participants in a relaxed, supine, fasting state to minimize external influences on autonomic function. Time-domain parameters including the standard deviation of normal-to-normal intervals (SDNN) and the root mean square of successive differences (RMSSD) were calculated. Frequency-domain indices such as low frequency (LF), high frequency (HF), and the LF/HF ratio were also determined. HRV data were analyzed using Kubios HRV Standard software, version 3.5.

Statistical Analysis: Data analysis was conducted using IBM SPSS Statistics software, version 25. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) for skewed data. Categorical variables were summarized using frequencies and percentages. Correlation analysis between adipokines, cardiac biomarkers, and HRV indices was carried out using Pearson correlation for normally distributed variables and Spearman rank correlation for non-normally distributed variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table- 1 outlines the demographic and clinical features of the 100 patients diagnosed with metabolic syndrome. The mean age of participants was 52.3 years (±8.4), with a male predominance (56 males and 44 females). The average body mass index (BMI) was 31.6 ± 4.3 kg/m², indicating that most participants were obese. Similarly, the mean waist circumference was 98.2 ± 9.7 cm, exceeding the IDF-defined thresholds for central obesity in both sexes. Lifestyle risk factors were notable, with 35% of the cohort being active smokers. A significant proportion of patients (62%) had coexisting hypertension, further compounding their cardiovascular risk. Biochemical assessments revealed a mean fasting blood glucose level of 123.5 ± 21.8 mg/dL, suggesting impaired glucose metabolism across the sample. Mean serum triglycerides were elevated at 181.4 ± 36.5 mg/dL, while HDL-cholesterol levels were low, averaging 38.9 ± 7.6 mg/dL. These values are consistent with the diagnostic profile of metabolic syndrome and highlight a pattern of substantial cardiometabolic dysregulation. The statistical analysis confirmed that differences in BMI, waist circumference, glucose, lipids, and hypertension status were all significant ($p < 0.05$), reinforcing the high-risk profile of this population.

Table 1: Demographic and Clinical Characteristics of the Study Population (n = 100)

Variable	Mean ± SD / n (%)	p-value*
Age (years)	52.3 ± 8.4	–
Gender (Male/Female)	56 / 44	–
Body Mass Index (kg/m²)	31.6 ± 4.3	0.001
Waist Circumference (cm)	98.2 ± 9.7	0.002
Smokers	35 (35%)	0.035
Hypertension	62 (62%)	0.008
Fasting Blood Glucose (mg/dL)	123.5 ± 21.8	0.000
Triglycerides (mg/dL)	181.4 ± 36.5	0.001
HDL-Cholesterol (mg/dL)	38.9 ± 7.6	0.004

*P-values indicate level of significance in differences compared to standard healthy values

Table- 2 presents the mean serum concentrations of key adipokines and cardiac biomarkers in patients with metabolic syndrome. Leptin levels were notably elevated, with a mean of 18.6 ± 5.7 ng/mL, reflecting the hyperleptinemic state commonly observed in obese individuals with insulin resistance. In contrast, adiponectin levels were significantly reduced (6.2 ± 1.9 μg/mL), consistent with its known inverse relationship with obesity and metabolic dysregulation. Resistin, another pro-inflammatory adipokine, showed an elevated mean value of 11.3 ± 3.1 ng/mL, supporting its role in systemic inflammation and cardiovascular risk in MetS.

Cardiac-specific biomarkers revealed early signs of myocardial strain and subclinical dysfunction. Troponin I, although within the normal diagnostic range, had a slightly raised mean value of 0.017 ± 0.006 ng/mL, indicating subtle myocardial injury. NT-proBNP levels, a marker of ventricular wall stress, averaged 135.4 ± 38.6 pg/mL, suggestive of increased cardiac workload even in the absence of overt heart failure. Similarly, CK-MB, an enzyme indicative of myocardial cell turnover, was moderately elevated at 22.8 ± 6.4 U/L. All the biomarkers demonstrated statistically significant deviations from reference ranges ($p < 0.05$), underscoring the pathophysiological burden of metabolic syndrome on both the endocrine and cardiovascular systems. These findings reinforce the interconnected nature of adipose dysfunction and early myocardial stress in this patient group.

Table 2: Serum Adipokine and Cardiac Biomarker Levels

Biomarker	Mean ± SD	p-value
Leptin (ng/mL)	18.6 ± 5.7	0.001
Adiponectin (μg/mL)	6.2 ± 1.9	0.003
Resistin (ng/mL)	11.3 ± 3.1	0.002
Troponin I (ng/mL)	0.017 ± 0.006	0.004
NT-proBNP (pg/mL)	135.4 ± 38.6	0.001
CK-MB (U/L)	22.8 ± 6.4	0.003

Table- 3 illustrates the autonomic nervous system function in patients with metabolic syndrome through analysis of heart rate variability (HRV) parameters. The mean standard deviation of normal-to-normal intervals (SDNN) was 35.4 ± 10.6 milliseconds, which is significantly lower than values seen in healthy individuals and indicative of reduced overall autonomic flexibility. The root mean square of successive differences (RMSSD), a marker of parasympathetic (vagal) activity, also showed a diminished mean value of 22.9 ± 8.7 ms, reflecting impaired parasympathetic modulation.

In the frequency domain analysis, the low-frequency (LF) component, representing both sympathetic and parasympathetic activity, averaged 620.3 ± 134.5 ms², while the high-frequency (HF) component, associated primarily with vagal tone, averaged 430.7 ± 112.6 ms². Both values were below normative thresholds, supporting the presence of autonomic imbalance. The LF/HF ratio, a key index of sympathovagal balance, was elevated at 1.53 ± 0.44, further confirming a shift toward sympathetic dominance.

These statistically significant abnormalities ($p < 0.05$) in HRV parameters suggest that patients with metabolic syndrome experience notable autonomic dysregulation. This pattern of reduced vagal tone and heightened sympathetic activity may contribute to increased cardiovascular risk, arrhythmia susceptibility, and poor cardiac adaptability in this high-risk population.

Table 3: Heart Rate Variability (HRV) Parameters

HRV Parameter	Mean ± SD	p-value
SDNN (ms)	35.4 ± 10.6	0.001
RMSSD (ms)	22.9 ± 8.7	0.002
Low Frequency (LF, ms²)	620.3 ± 134.5	0.003
High Frequency (HF, ms²)	430.7 ± 112.6	0.005
LF/HF Ratio	1.53 ± 0.44	0.001

Table 4 presents the correlation analysis exploring the associations between serum adipokines and both cardiac biomarkers and heart rate variability (HRV) indices in patients with metabolic syndrome. A statistically significant positive correlation was observed between leptin and troponin I ($r = 0.36$, $p = 0.001$), indicating that elevated leptin levels may be linked to subclinical myocardial injury. Similarly, resistin showed a positive correlation with CK-MB ($r = 0.33$, $p = 0.003$), suggesting an inflammatory contribution to myocardial stress or cell turnover.

Conversely, adiponectin, known for its anti-inflammatory and cardioprotective effects, demonstrated a strong inverse correlation with NT-proBNP ($r = –0.42$, $p = 0.002$), indicating that lower adiponectin levels are associated with increased ventricular strain. Regarding autonomic function, leptin levels were positively correlated with the LF/HF ratio ($r = 0.41$, $p = 0.001$), implying a leptin-driven shift toward sympathetic overactivity. In contrast, adiponectin was inversely correlated with SDNN ($r = –0.38$, $p = 0.004$), further supporting its role in modulating autonomic balance.

All correlations were statistically significant ($p < 0.05$), highlighting a complex and biologically meaningful interplay between adipose-derived signaling molecules, cardiac stress markers, and autonomic dysfunction in metabolic syndrome. These relationships underscore the potential utility of integrated biomarker profiling for early cardiovascular risk assessment in affected individuals.

Table 4: Correlation between Adipokines and Cardiac Biomarkers/HRV Parameters

Parameter Pair	Correlation Coefficient (r)	p-value
Leptin vs Troponin I	0.36*	0.001
Adiponectin vs NT-proBNP	–0.42*	0.002
Resistin vs CK-MB	0.33*	0.003
Leptin vs LF/HF Ratio	0.41*	0.001
Adiponectin vs SDNN	–0.38*	0.004

*All correlations statistically significant at $p < 0.05$.

DISCUSSION

This study provided a comprehensive evaluation of the interrelationship between adipokine dysregulation, cardiac stress biomarkers, and autonomic nervous system function in patients with metabolic syndrome (MetS). The findings affirm the multifactorial nature of MetS and highlight a biologically interconnected pathway that links metabolic disturbances with subclinical cardiovascular dysfunction and autonomic imbalance[18]. The observed elevation in leptin and resistin levels, alongside reduced adiponectin, aligns with existing literature describing the pro-inflammatory and atherogenic roles of adipokines in MetS. Leptin, beyond its metabolic regulatory functions, has been implicated in sympathetic overactivity and vascular endothelial dysfunction, both of which can predispose individuals to hypertension and left ventricular hypertrophy. The positive correlation found between leptin and troponin I, as well as with LF/HF ratio, supports the hypothesis that leptin may serve as a biochemical mediator linking central obesity with myocardial strain and autonomic dysregulation[19, 20].

Similarly, elevated resistin levels in our cohort are consistent with previous studies demonstrating its role in promoting insulin resistance, systemic inflammation, and endothelial injury. Adiponectin, known for its anti-inflammatory and vasoprotective

properties, showed significantly lower serum concentrations in the study population[21]. Its inverse correlation with NT-proBNP and SDNN suggests that diminished adiponectin not only reflects metabolic impairment but also corresponds with early cardiac stress and reduced parasympathetic tone. These findings are particularly concerning, given the known association between autonomic dysfunction manifested as reduced HRV and increased risk of sudden cardiac death, arrhythmias, and myocardial infarction[22].

Cardiac biomarkers, including NT-proBNP and CK-MB, were mildly but significantly elevated, indicating underlying myocardial stress despite the absence of overt cardiovascular disease in our cohort. The subtle elevation in troponin I levels further reinforces the notion of subclinical myocardial injury potentially driven by metabolic and autonomic stressors[23]. The use of these biomarkers in combination with adipokines provides a more nuanced understanding of the cardiovascular phenotype in MetS, suggesting that traditional clinical parameters alone may underestimate risk. The HRV data revealed a clear pattern of autonomic imbalance, with reductions in SDNN, RMSSD, and HF, along with elevated LF/HF ratios findings indicative of increased sympathetic activity and diminished parasympathetic modulation[24].

This pattern not only reflects altered autonomic regulation but also implies compromised cardiovascular adaptability, particularly under stress conditions. Such dysfunction may represent an early warning sign for future cardiovascular events[25]. Taken together, these results underscore the importance of a multidimensional approach to risk assessment in patients with metabolic syndrome. The simultaneous evaluation of adipokines, cardiac biomarkers, and autonomic function offers valuable insights into the complex pathophysiological mechanisms that precede overt cardiovascular disease. This integrative model could facilitate earlier identification of high-risk individuals and inform targeted interventions aimed at modulating inflammatory, metabolic, and autonomic pathways[26].

However, this study has limitations, including its cross-sectional design, which restricts causal inference, and the lack of a healthy control group for comparative analysis. Longitudinal studies are warranted to determine the predictive value of these biomarkers for future cardiovascular outcomes in patients with MetS. Additionally, further exploration into sex-specific differences and the impact of pharmacologic interventions on these biomarkers may enhance clinical applicability[27].

CONCLUSION

The present study highlights a significant and biologically plausible association between adipokine imbalance, cardiac stress markers, and autonomic dysfunction in metabolic syndrome. These findings advocate for the integration of biomarker-based screening tools in routine clinical evaluation to improve cardiovascular risk stratification and guide early preventive strategies in this high-risk population.

Availability of Data: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests: The authors declare that they have no competing interests.

Funding: No funding was received from any public, private, or commercial entity for the conduct of this study.

Authors' Contributions: Z.A.N. contributed to study design and manuscript drafting. S.L.P. assisted in clinical data collection. A.H. coordinated biochemical analysis. S.N.Z. performed statistical analysis and interpretation. A.A. conceptualized the study and served as the corresponding author. A.E. contributed to data entry and literature review. All authors read and approved the final manuscript.

Acknowledgments: The authors sincerely thank the clinical, laboratory, and administrative staff for their valuable support and cooperation throughout the study.

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This article may be cited as: Nabi ZA, Prithiani SL, Hameed A, Zehra SN, Anjum A, Ejaz A: Integrated Evaluation of Adipokines, Cardiac Biomarkers, and Autonomic Nervous System Activity in Patients with Metabolic Syndrome: A Cross-Sectional Clinical Study. Pak J Med Health Sci, 2023; 17(10): 200-204.