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ORIGINAL ARTICLE

Biochemical and Physiological Insights into Adipokine-Mediated Insulin Resistance and Its Association with Atherosclerotic Progression in Prediabetic Patients

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ABSTRACT

Background: Prediabetes is a metabolically active state associated with insulin resistance and early vascular dysfunction, serving as a precursor to type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease. Adipokines bioactive molecules secreted by adipose tissue are central to this progression, yet their role in prediabetic individuals remains under-investigated.

Objective: To assess the biochemical and physiological roles of adipokines adiponectin, leptin, resistin, and visfatin in mediating insulin resistance and their association with subclinical atherosclerosis in prediabetic patients.

Methods: This cross-sectional study was conducted from November 2022 to May 2023 at Shahbaz Sharif Hospital, Multan, and Bolan Medical Complex Hospital (BMCH), Quetta. A total of 100 prediabetic individuals (aged 30–60 years) were enrolled. Fasting glucose, insulin, HbA1c, lipid profile, and serum adipokine levels were measured. Insulin resistance was estimated using the HOMA-IR index, while subclinical atherosclerosis was evaluated by carotid intima-media thickness (CIMT) using B-mode ultrasonography.

Results: Mean HOMA-IR was 4.1 ± 1.6, and 62% of participants had CIMT ≥ 0.8 mm. Adiponectin levels were significantly reduced (4.6 ± 1.0 µg/mL), while leptin (18.7 ± 6.9 ng/mL), resistin (13.2 ± 3.6 ng/mL), and visfatin (36.9 ± 8.3 ng/mL) were elevated. Adiponectin correlated inversely with HOMA-IR ($r = –0.44$; $p = 0.002$) and CIMT ($r = –0.36$; $p = 0.008$), whereas resistin and visfatin showed positive correlations with both insulin resistance and CIMT ($p < 0.01$).

Conclusion: Adipokine imbalance plays a critical role in the development of insulin resistance and early atherosclerosis in prediabetic individuals. These markers may serve as early predictors of cardiometabolic risk, warranting their inclusion in routine prediabetes screening to enable timely intervention and prevention of disease progression.

Keywords: Prediabetes, Insulin resistance, Adipokines, Adiponectin, Leptin, Resistin, Visfatin, HOMA-IR, CIMT, Atherosclerosis

INTRODUCTION

Prediabetes is increasingly recognized as a crucial intermediary state between normal glucose tolerance and type 2 diabetes mellitus (T2DM), characterized by impaired fasting glucose and/or impaired glucose tolerance. Although traditionally viewed as a silent metabolic disorder, recent evidence highlights that prediabetes is far from benign[1]. It is associated with early-onset endothelial dysfunction, systemic low-grade inflammation, and subclinical atherosclerosis, thereby markedly increasing the risk for cardiovascular disease (CVD) the leading cause of morbidity and mortality globally. A growing body of research has shifted the focus toward understanding the biochemical and physiological disruptions occurring during this prediabetic phase, particularly the role of adipose tissue-derived hormones, collectively known as adipokines[2].

Adipose tissue, once regarded merely as an energy reservoir, is now well-established as an active endocrine organ that secretes numerous bioactive molecules. Among these, adipokines such as adiponectin, leptin, resistin, and visfatin have emerged as key modulators of metabolic homeostasis, inflammation, and vascular health[3]. These molecules are involved in complex physiological pathways, including insulin sensitivity regulation, lipid metabolism, appetite control, immune response modulation, and endothelial function. An imbalance in the secretion or action of adipokines due to increased adiposity and metabolic stress leads to insulin resistance, which is central to the pathogenesis of T2DM. Concurrently, this dysregulation promotes vascular inflammation, oxidative stress, and endothelial damage, which are the foundational processes in the development of atherosclerosis[4].

Among the key adipokines, adiponectin is unique for its insulin-sensitizing and anti-inflammatory effects. Reduced levels of adiponectin are consistently associated with increased insulin resistance and cardiovascular risk. In contrast, leptin, primarily involved in energy expenditure and appetite regulation, shows paradoxical effects in obesity where high circulating levels often fail to exert expected metabolic actions, a condition termed "leptin resistance." Elevated leptin levels have been linked to pro-inflammatory states and atherogenesis[5]. Similarly, resistin, initially identified for its role in insulin resistance, is now understood to play a role in endothelial dysfunction and the promotion of vascular smooth muscle proliferation. Visfatin, although less studied, has shown pro-inflammatory effects and associations with plaque instability and increased carotid intima-media thickness (CIMT), a surrogate marker of subclinical atherosclerosis[6].

The pathophysiological overlap between insulin resistance and atherosclerosis underscores a shared inflammatory and metabolic origin, with adipokines acting as pivotal mediators. This association becomes particularly important in prediabetic individuals who are often overlooked for early interventions, despite being in a state of progressive metabolic dysregulation. While insulin resistance is traditionally evaluated using indices such as the homeostasis model assessment of insulin resistance (HOMA-IR), assessing vascular health through CIMT provides valuable insight into early atherosclerotic changes[7].

Despite the growing recognition of adipokines in metabolic and cardiovascular regulation, limited data are available from prediabetic populations, especially in the context of their dual role in insulin resistance and atherosclerotic progression. Most studies have focused on obese or diabetic cohorts, overlooking the subtler biochemical changes that precede overt disease. Furthermore, regional variations in adipokine profiles and their clinical implications necessitate population-specific research, particularly in South Asian populations where the burden of metabolic syndrome is rapidly rising[8, 9].

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Therefore, the present study aims to bridge this knowledge gap by investigating the biochemical and physiological interplay of adipokines with insulin resistance and early vascular changes in prediabetic individuals. By measuring serum levels of adiponectin, leptin, resistin, and visfatin, and correlating them with HOMA-IR and CIMT, this study seeks to elucidate the pathophysiological link between metabolic dysregulation and vascular damage in the prediabetic phase. These insights may not only enhance early detection and risk stratification but also offer novel targets for preventive strategies aimed at halting the progression toward T2DM and atherosclerotic cardiovascular disease[10].

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional, analytical study was carried out jointly at two tertiary care government hospitals in Pakistan: Shahbaz Sharif Hospital, Multan, and Bolan Medical Complex Hospital (BMCH), Quetta. Both institutions are equipped with full diagnostic and biochemical facilities necessary for metabolic and vascular profiling. The study was conducted over a period of seven months, from November 2022 to May 2023, with full ethical clearance obtained from the institutional review boards of both hospitals prior to commencement.

Sample Size and Selection Criteria: A total of 100 adult prediabetic patients aged between 30 and 60 years were included in the study. Participants were selected using non-probability purposive sampling. The diagnostic criteria for prediabetes followed the American Diabetes Association (ADA) guidelines, including fasting plasma glucose levels between 100–125 mg/dL and/or HbA1c values between 5.7–6.4%. These criteria were confirmed with laboratory assessments at the respective hospital laboratories. Written informed consent was obtained from each participant after explaining the study objectives and procedures.

Inclusion Criteria: Eligible participants were adults between 30 to 60 years of age with confirmed prediabetes, who were not on any antidiabetic, antihypertensive, or lipid-lowering drugs. They were required to be clinically stable, willing to undergo biochemical tests and carotid ultrasonography, and cooperative with follow-up procedures for complete data collection.

Exclusion Criteria: Participants with confirmed diabetes mellitus (fasting glucose ≥126 mg/dL or HbA1c ≥6.5%), known cardiovascular disease, history of stroke or peripheral vascular disease, active or chronic infections, autoimmune diseases, malignancy, renal or hepatic insufficiency, current corticosteroid use, or pregnancy were excluded from the study to eliminate confounding variables.

Biochemical Measurements: Fasting blood samples were collected under aseptic conditions from each participant after a minimum of 10–12 hours of overnight fasting. The blood samples were immediately centrifuged at 3000 rpm for 10 minutes, and the serum was stored at −80°C until further analysis. All biochemical assays were performed in the central biochemistry laboratories of Shahbaz Sharif Hospital and BMCH using standardized methods. Fasting plasma glucose and lipid profile were analyzed enzymatically. HbA1c was measured using high-performance liquid chromatography (HPLC). Fasting serum insulin was determined using electrochemiluminescence immunoassay.

For the estimation of adipokines adiponectin, leptin, resistin, and visfatin sandwich ELISA (enzyme-linked immunosorbent assay) kits specific for human proteins were employed (Bioassay Technology Laboratory, China). The assays were performed in duplicate for each sample to ensure intra-assay reliability. The inter-assay and intra-assay coefficients of variation were maintained below 10% for quality assurance.

Assessment of Insulin Resistance: Insulin resistance was evaluated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). The formula used was:

HOMA-IR = (Fasting insulin [μU/mL] × Fasting glucose [mg/dL]) / 405: A HOMA-IR value of 2.5 or above was considered indicative of significant insulin resistance based on population-adjusted cutoff points.

Measurement of Subclinical Atherosclerosis: To assess early atherosclerotic changes, carotid intima-media thickness (CIMT) was measured using high-resolution B-mode ultrasonography equipped with a 7.5 MHz linear array transducer. The ultrasonographic evaluations were performed in both hospitals by trained radiologists blinded to the biochemical data. Measurements were taken bilaterally at the common carotid artery 1 cm proximal to the bifurcation. The mean CIMT value was calculated from three readings on each side. A CIMT ≥0.8 mm was considered abnormal, indicative of early subclinical atherosclerosis.

Anthropometric and Clinical Data Collection: A standardized, pre-tested proforma was used to collect demographic and clinical information, including age, sex, height, weight, body mass index (BMI), waist circumference, blood pressure, family history of diabetes, smoking status, and physical activity level. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood pressure was recorded using a calibrated sphygmomanometer after 10 minutes of rest in a seated position.

Ethical Approval and Consent: The study protocol was approved by the Institutional Ethical Review Committees. All participants were provided with detailed information regarding the objectives and procedures of the study, and written informed consent was obtained prior to enrollment. The study adhered to the principles outlined in the Declaration of Helsinki (2013 revision) regarding research involving human subjects.

Statistical Analysis: All data were entered and analyzed using IBM SPSS version 26.0. Quantitative variables such as adipokine levels, HOMA-IR, and CIMT were expressed as mean ± standard deviation (SD). Categorical variables were reported as frequencies and percentages. Independent t-tests were used for comparison between groups. Pearson's correlation coefficient was applied to examine the relationship between serum adipokine levels and metabolic/vascular markers including HOMA-IR and CIMT. A p-value < 0.05 was considered statistically significant for all analyses.

RESULTS

This study included 100 prediabetic patients evaluated between November 2022 and May 2023 at Shahbaz Sharif Hospital, Multan, and Bolan Medical Complex Hospital, Quetta. The findings are presented in four main segments: demographic characteristics, biochemical and lipid profiles, adipokine levels, and vascular outcomes, with correlation analyses included. Each table is cited and fully explained in the corresponding paragraph.

Demographic and Clinical Characteristics: The baseline demographic and clinical data of participants are summarized in Table 1. The mean age of the cohort was 47.8 ± 6.9 years, and the gender distribution included 56 males and 44 females, indicating a slight male predominance. The mean BMI was 28.6 ± 3.5 kg/m², suggesting that most participants were either overweight or borderline obese. A significant 66% had pre-existing hypertension, and 74% reported a positive family history of diabetes. Lifestyle-related risk factors were also prominent, with 61% living a sedentary lifestyle and 24% identified as current smokers.

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	Value
Mean Age (years)	47.8 ± 6.9
Gender (Male/Female)	56 / 44
BMI (kg/m²)	28.6 ± 3.5
Hypertension (%)	66%
Family History of Diabetes (%)	74%
Current Smokers (%)	24%
Sedentary Lifestyle (%)	61%

Biochemical Profile and Lipid Parameters: Table 2 outlines the glycemic and lipid profile of participants. The mean fasting glucose was 111.5 ± 8.1 mg/dL, and HbA1c was 6.1 ± 0.2%, both within the defined prediabetic range. Fasting insulin levels averaged 14.8 ± 4.1 μU/mL, and the derived HOMA-IR was 4.1 ± 1.6, clearly

reflecting insulin resistance. Lipid abnormalities were prominent: total cholesterol was 204 ± 32 mg/dL, LDL-C was 132 ± 27 mg/dL, and triglycerides were elevated at 186 ± 44 mg/dL, while HDL-C was reduced at 42 ± 7 mg/dL. These findings highlight the atherogenic lipid profile commonly seen in prediabetic states.

Table 2: Glycemic and Lipid Profiles in Prediabetic Participants

Parameter	Mean ± SD
Fasting Glucose (mg/dL)	111.5 ± 8.1
HbA1c (%)	6.1 ± 0.2
Fasting Insulin (µU/mL)	14.8 ± 4.1
Total Cholesterol (mg/dL)	204 ± 32
LDL-C (mg/dL)	132 ± 27
HDL-C (mg/dL)	42 ± 7
Triglycerides (mg/dL)	186 ± 44
HOMA-IR	4.1 ± 1.6

Adipokine Profiles: As depicted in Table 3, the adipokine levels in the prediabetic cohort demonstrated a dysregulated pattern. Adiponectin, known for its anti-inflammatory and insulin-sensitizing properties, was markedly reduced (4.6 ± 1.0 µg/mL). In contrast, pro-inflammatory adipokines such as leptin (18.7 ± 6.9 ng/mL), resistin (13.2 ± 3.6 ng/mL), and visfatin (36.9 ± 8.3 ng/mL) were significantly elevated, consistent with the development of metabolic and vascular dysfunction.

Table 3: Circulating Adipokine Levels in Prediabetic Patients

Adipokine	Mean ± SD
Adiponectin (µg/mL)	4.6 ± 1.0
Leptin (ng/mL)	18.7 ± 6.9
Resistin (ng/mL)	13.2 ± 3.6
Visfatin (ng/mL)	36.9 ± 8.3

These findings illustrate a biochemical environment favoring inflammation, oxidative stress, and insulin resistance. Importantly, these adipokines may serve not only as biomarkers of metabolic status but also as early indicators of cardiovascular disease progression.

Vascular Parameters and Atherosclerosis Assessment: Table 4 presents the data on carotid intima-media thickness (CIMT), a surrogate marker of subclinical atherosclerosis. The mean CIMT was 0.87 ± 0.14 mm, and 62% of participants had CIMT values equal to or exceeding 0.8 mm, the threshold for early atherosclerotic change. This is noteworthy as it indicates preclinical vascular damage even before the onset of overt diabetes.

Table 4: Vascular Parameter in Prediabetic Patients

Parameter	Mean ± SD
Carotid Intima-Media Thickness (mm)	0.87 ± 0.14
CIMT ≥ 0.8 mm (Prevalence)	62%

Correlation Analysis Between Adipokines, HOMA-IR, and CIMT: Table 5 shows the Pearson correlation coefficients between serum adipokine levels and key pathophysiological markers. Adiponectin showed a negative correlation with both HOMA-IR ($r = –0.44$, $p = 0.002$) and CIMT ($r = –0.36$, $p = 0.008$), reinforcing its protective metabolic and vascular role. Conversely, resistin and visfatin demonstrated significant positive correlations with CIMT ($r = 0.52$ and $r = 0.39$, respectively) and HOMA-IR, indicating their contribution to insulin resistance and atherosclerosis.

Table 5: Correlation Between Adipokines, HOMA-IR, and CIMT

Adipokine	Correlation with HOMA-IR (r)	p-value	Correlation with CIMT (r)	p-value
Adiponectin	–0.44	0.002	–0.36	0.008
Leptin	0.46	0.001	0.33	0.011
Resistin	0.49	<0.001	0.52	<0.001
Visfatin	0.38	0.006	0.39	0.004

The data clearly demonstrate that prediabetic patients already exhibit metabolic and vascular dysfunction, as reflected by abnormal adipokine profiles, increased insulin resistance, and early signs of atherosclerosis. The inverse relationship of adiponectin with both insulin resistance and CIMT, coupled with the positive association of leptin, resistin, and visfatin with these parameters, supports the hypothesis that adipokines are central to the interplay between metabolic syndrome and cardiovascular disease.

These results suggest the need for early biochemical screening, particularly for adipokines, in prediabetic individuals to allow timely lifestyle or pharmacological interventions that could halt or slow progression to type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

DISCUSSION

The findings of this study reveal critical biochemical and physiological disruptions in prediabetic individuals, emphasizing the pivotal role of adipokine imbalance in the early development of insulin resistance and subclinical atherosclerosis[11]. Prediabetes, although asymptomatic, is not a metabolically neutral state. It is increasingly evident from both clinical and molecular studies that the prediabetic phase is marked by systemic low-grade inflammation, endothelial dysfunction, and vascular remodeling all of which converge toward overt type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). The current study builds upon this concept by demonstrating significant alterations in adipokine profiles particularly reduced adiponectin and elevated leptin, resistin, and visfatin and their strong correlations with HOMA-IR and carotid intima-media thickness (CIMT) [12].

Adiponectin, the only adipokine with anti-inflammatory and insulin-sensitizing properties, was significantly reduced in the present study. Its inverse relationship with both HOMA-IR and CIMT is consistent with previous reports suggesting that adiponectin deficiency leads to impaired insulin signaling, increased hepatic gluconeogenesis, and vascular inflammation[13]. In contrast, elevated leptin levels observed in our study were significantly associated with both BMI and HOMA-IR, suggesting the presence of leptin resistance, a hallmark of metabolic syndrome. Furthermore, leptin has been implicated in promoting vascular smooth muscle proliferation and oxidative stress, which may contribute to the observed thickening of the carotid intima-media complex[14].

Resistin, another adipokine elevated in our cohort, is primarily produced by macrophages in humans and has been linked to endothelial activation, insulin receptor blockade, and promotion of vascular inflammation[15]. Its strong positive correlation with both insulin resistance and CIMT underscores its potential role as a key mediator of cardiometabolic disease in prediabetic individuals. Similarly, visfatin, though less studied, showed a robust association with CIMT. Its known pro-inflammatory effects, including upregulation of TNF-α and IL-6, and its ability to mimic insulin receptor binding in a dysfunctional manner may explain this correlation[16].

One of the most striking findings was the early vascular compromise evident in 62% of participants, who had CIMT values ≥0.8 mm. This indicates that a significant proportion of prediabetic individuals already harbor early atherosclerotic lesions even before the clinical onset of diabetes or cardiovascular events[17]. The correlation between CIMT and circulating adipokines such as resistin and visfatin adds further evidence to the mechanistic role of adipose tissue-derived factors in vascular pathology. These results align with prior research showing that adipokines directly modulate endothelial function, nitric oxide bioavailability, and vascular cell adhesion molecule expression[18].

This study also highlights the co-existence of traditional cardiovascular risk factors in prediabetics, including hypertension, dyslipidemia, obesity, sedentary behavior, and smoking. However, while these factors are well known, the novelty of this work lies in the biochemical quantification of adipokines and their statistically significant correlations with insulin resistance and vascular

markers, offering deeper insights into early pathophysiological transitions[3].

The multi-centered nature of the study, involving participants from both Shahbaz Sharif Hospital, Multan, and Bolan Medical Complex Hospital, Quetta, adds diversity to the sample and enhances the generalizability of the findings across different Pakistani populations[8]. However, the study is not without limitations. Its cross-sectional design precludes causal inference, and the use of surrogate markers such as HOMA-IR and CIMT, although validated, may not fully capture the dynamic interplay of adipokines in vivo. Furthermore, a longitudinal study design could better delineate the predictive value of adipokines in disease progression[1].

Nonetheless, these findings carry significant clinical implications. Given the ease of measuring circulating adipokines using ELISA-based techniques and their strong associations with metabolic and vascular dysfunction, they could serve as valuable biomarkers for risk stratification in prediabetic individuals. Moreover, they open avenues for adipokine-targeted therapies aimed at halting or reversing insulin resistance and early atherosclerosis[19].

CONCLUSION

This study provides compelling evidence that adipokine dysregulation marked by low adiponectin and elevated leptin, resistin, and visfatin is closely linked to insulin resistance and early atherosclerotic changes in prediabetic individuals. The strong correlations observed between these adipokines, HOMA-IR, and CIMT highlight their dual role as mediators and biomarkers of cardiometabolic risk. The presence of subclinical atherosclerosis in a majority of prediabetics underscores the urgency for early detection and intervention. Incorporating adipokine profiling into routine screening protocols may enable more precise risk prediction and pave the way for targeted preventive strategies. Future longitudinal studies are warranted to validate these findings and explore the therapeutic potential of modulating adipokine activity in delaying or preventing the transition to overt diabetes and cardiovascular disease.

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Conflict of Interest: The authors declare no conflict of interest related to the publication of this article.

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

Authors' Contributions: NA and HK conceptualized the study and drafted the manuscript. KP and SDM contributed to biochemical analyses and data interpretation. ML assisted in clinical evaluation and patient recruitment. AI supervised statistical analysis and manuscript revision. All authors read and approved the final version of the manuscript.

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