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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: Insulin resistance is a key metabolic abnormality in prediabetes that contributes to the development of type 2 diabetes mellitus (T2DM) and accelerates atherosclerosis. Adipose tissue functions as an endocrine organ, secreting adipokines that regulate insulin sensitivity, vascular function, and inflammation. Altered adipokine profiles may provide mechanistic links between prediabetes and early atherosclerotic changes.

Objectives: To investigate the biochemical and physiological insights into adipokine-mediated insulin resistance and its association with atherosclerotic progression in prediabetic patients.

Methodology: This cross-sectional study was conducted from December 2022 to August 2023 at Nawaz Shareef Medical College, Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and Chahudhary Pervaiz Elahi Institute of Cardiology, Wazirabad. A total of 100 prediabetic patients were enrolled. Demographic data, anthropometric measurements, and blood pressure were recorded. Fasting glucose, insulin, lipid profile, hs-CRP, adiponectin, leptin, resistin, visfatin, and TNF-α were measured. Insulin resistance was assessed using HOMA-IR. Carotid intima-media thickness (CIMT) was determined by B-mode ultrasonography. Statistical analysis included correlation and regression models.

Results: Participants had elevated HOMA-IR, dyslipidemia, and raised hs-CRP. Adiponectin levels were significantly reduced, while leptin, resistin, visfatin, and TNF-α were increased. CIMT was higher in 28% of patients, indicating early atherosclerosis. Adiponectin showed an inverse correlation with CIMT, whereas leptin, resistin, visfatin, TNF-α, and hs-CRP correlated positively.

Conclusion: Prediabetic patients demonstrate a dysregulated adipokine profile and inflammatory state that are strongly associated with early subclinical atherosclerosis. Monitoring adipokines may serve as an early tool for cardiovascular risk stratification and prevention in high-risk populations.

Keywords: Prediabetes; Insulin resistance; Adipokines; Atherosclerosis; Inflammation; Carotid intima-media thickness

INTRODUCTION

Insulin resistance is a central metabolic abnormality that predisposes individuals to the development of type 2 diabetes mellitus (T2DM) and contributes significantly to cardiovascular morbidity and mortality. Among patients at the prediabetic stage, subtle alterations in glucose metabolism are accompanied by biochemical and physiological changes that accelerate vascular injury and atherosclerosis [5]. Adipose tissue, once considered merely an energy reservoir, is now recognized as an active endocrine organ that secretes a wide range of bioactive molecules termed adipokines, including adiponectin, leptin, resistin, visfatin, and tumor necrosis factor-alpha (TNF-α). These adipokines exert profound effects on insulin sensitivity, glucose homeostasis, lipid metabolism, and vascular endothelial function, thereby linking metabolic dysregulation with cardiovascular pathology [1-3].

Emerging evidence suggests that altered adipokine profiles in prediabetic patients play a pivotal role in promoting insulin resistance through inflammatory, oxidative stress, and endothelial dysfunction pathways. Reduced adiponectin levels impair insulin-mediated glucose uptake, whereas elevated leptin and resistin concentrations are associated with low-grade systemic inflammation and impaired vascular relaxation [4]. Such imbalances not only disrupt metabolic regulation but also create a pro-atherogenic environment that fosters arterial wall thickening, lipid deposition, and plaque progression. Consequently, the interaction between adipokines and insulin resistance serves as a critical mechanistic bridge between prediabetes and early atherosclerotic disease [6] .

The global rise in obesity and metabolic syndrome has led to an alarming increase in prediabetes prevalence, particularly in South Asian countries, including Pakistan, where genetic predisposition, dietary habits, and sedentary lifestyles intensify the risk.[7,8] Importantly, patients at the prediabetic stage are often asymptomatic, yet they demonstrate early endothelial dysfunction and subclinical atherosclerosis detectable through biomarkers and imaging modalities.[9] Early identification of adipokine-mediated pathways provides a unique opportunity to stratify cardiovascular risk and initiate preventive interventions before progression to overt diabetes or advanced atherosclerotic disease.[10]

Given this background, the present study was conducted to investigate the biochemical and physiological insights into adipokine-mediated insulin resistance and its association with atherosclerotic progression in prediabetic patients. A total of 100 patients were enrolled from Nawaz Shareef Medical College, Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and Chahudhary Pervaiz Elahi Institute of Cardiology, Wazirabad, Pakistan, between December 2022 and August 2023. This work aims to elucidate the mechanistic links between altered adipokine levels, insulin resistance, and early atherosclerotic changes, thereby contributing to a better understanding of cardiometabolic risk stratification in prediabetic individuals.

MATERIALS AND METHODS

This cross-sectional observational study was conducted between December 2022 and August 2023 at Nawaz Shareef Medical College, Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and Chahudhary Pervaiz Elahi Institute of Cardiology, Wazirabad, Pakistan. A total of 100 prediabetic patients were recruited using non-probability consecutive sampling. Prediabetes was defined according to the American Diabetes Association criteria, including impaired fasting glucose (100–125 mg/dL) and/or impaired glucose tolerance (2-hour plasma glucose 140–199 mg/dL). Patients with previously diagnosed type 2 diabetes mellitus, history of ischemic heart disease, chronic inflammatory conditions, or use of medications affecting glucose or lipid metabolism were excluded. Written informed consent was obtained from all participants, and

the study was approved by the institutional ethical review committee.

Demographic and clinical information, including age, sex, body mass index, waist circumference, systolic and diastolic blood pressure, smoking status, and family history of cardiovascular disease, were recorded through structured interviews and physical examination. Anthropometric measurements were performed using standardized protocols, with body mass index calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured in a seated position after five minutes of rest using a calibrated sphygmomanometer, and the average of two readings was considered.

Fasting blood samples were collected after an overnight fast of at least 10 hours. Serum glucose and insulin levels were measured to calculate the homeostasis model assessment of insulin resistance (HOMA-IR). Lipid profile, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, was analyzed using enzymatic methods. High-sensitivity C-reactive protein (hs-CRP) was measured as an inflammatory biomarker. Specific adipokines including adiponectin, leptin, resistin, and visfatin were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Tumor necrosis factor-alpha (TNF-α) was also measured as a pro-inflammatory cytokine.

To evaluate early atherosclerotic changes, carotid intima-media thickness (CIMT) was assessed using high-resolution B-mode ultrasonography by an experienced radiologist blinded to the clinical data. The mean of three measurements from the common carotid artery was taken as the representative CIMT value. All laboratory analyses were performed in the same institutional biochemistry laboratory to ensure standardization and quality control. Data were anonymized and stored securely for analysis.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables such as age, body mass index, blood pressure, lipid parameters, adipokine levels, and carotid intima-media thickness were expressed as mean ± standard deviation, while categorical variables such as sex, smoking status, and family history were presented as frequencies and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test. Independent sample t-test or Mann–Whitney U test was applied to compare continuous variables between groups, whereas chi-square test was used for categorical variables. Pearson or Spearman correlation analysis was performed to assess associations between adipokines, insulin resistance, and carotid intima-media thickness. Multivariate linear regression analysis was conducted to identify independent predictors of atherosclerotic progression after adjusting for potential confounders. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 100 prediabetic patients were included in the study, with 56 males and 44 females. The mean age of participants was 49.6 ± 7.8 years. The baseline demographic and clinical characteristics are presented in Table 1. Males had a slightly higher prevalence of smoking compared to females (28.6% vs. 11.4%), whereas obesity and family history of cardiovascular disease were more common among females. The mean body mass index of the overall cohort was 28.4 ± 3.9 kg/m², and the average waist circumference was 95.2 ± 8.7 cm. The mean systolic and diastolic blood pressures were 132.6 ± 14.2 mmHg and 84.1 ± 8.3 mmHg, respectively.

Table 1 presents the baseline demographic and clinical characteristics of the 100 prediabetic patients enrolled in the study. The mean age of the study population was 49.6 ± 7.8 years, with a slightly higher representation of males (56%) compared to females (44%). The average body mass index (BMI) was 28.4 ± 3.9 kg/m², falling within the overweight-to-obese category, with women showing marginally higher BMI values than men. Waist circumference and blood pressure levels were also elevated, reflecting the presence of central obesity and borderline hypertension in this group. A significantly higher prevalence of smoking was observed among males (28.6%) compared to females (11.4%), while family history of cardiovascular disease was reported in 37% of the cohort, more frequently among females. These findings indicate that the study population had a clustering of cardiometabolic risk factors that could contribute to accelerated atherosclerotic progression.

Table 1: Baseline demographic and clinical characteristics of prediabetic patients (n = 100)

Variable	Total (n=100)	Male (n=56)	Female (n=44)	p-value
Age (years)	49.6 ± 7.8	50.2 ± 8.1	48.8 ± 7.4	0.412
BMI (kg/m²)	28.4 ± 3.9	27.9 ± 3.7	29.1 ± 4.0	0.093
Waist circumference (cm)	95.2 ± 8.7	96.5 ± 9.2	93.6 ± 8.1	0.174
Systolic BP (mmHg)	132.6 ± 14.2	134.1 ± 13.7	130.7 ± 14.8	0.265
Diastolic BP (mmHg)	84.1 ± 8.3	84.9 ± 7.9	83.1 ± 8.8	0.352
Smoking (%)	21.0	28.6	11.4	0.041*
Family history of CVD (%)	37.0	32.1	43.2	0.241

*Significant at $p < 0.05$

Table 2: Biochemical and biomarker profile of prediabetic patients (n = 100)

Parameter	Mean ± SD	Reference/Normal Range
Fasting glucose (mg/dL)	112.4 ± 7.3	<100
Fasting insulin (µIU/mL)	14.2 ± 4.6	2–12
HOMA-IR	3.9 ± 1.1	<2.5
Total cholesterol (mg/dL)	202.8 ± 35.6	<200
LDL-C (mg/dL)	128.2 ± 28.3	<100
HDL-C (mg/dL)	39.5 ± 6.7	>40
Triglycerides (mg/dL)	178.6 ± 41.2	<150
hs-CRP (mg/L)	4.8 ± 1.7	<3
Adiponectin (µg/mL)	5.6 ± 1.9	10–30
Leptin (ng/mL)	21.3 ± 6.8	5–15
Resistin (ng/mL)	12.8 ± 4.2	4–8
Visfatin (ng/mL)	9.4 ± 3.1	2–6
TNF-α (pg/mL)	7.6 ± 2.4	<5

Biochemical analysis revealed that the mean fasting plasma glucose was 112.4 ± 7.3 mg/dL, and fasting insulin was 14.2 ± 4.6 µIU/mL, yielding an average HOMA-IR score of 3.9 ± 1.1, consistent with insulin resistance in this cohort. Lipid profile analysis showed elevated triglycerides (178.6 ± 41.2 mg/dL) and low HDL-C (39.5 ± 6.7 mg/dL), while mean LDL-C was 128.2 ± 28.3 mg/dL. High-sensitivity C-reactive protein (hs-CRP) was elevated in most patients, with a mean value of 4.8 ± 1.7 mg/L. Adipokine profiling demonstrated significantly reduced adiponectin levels and increased leptin, resistin, and visfatin levels, indicating a pro-inflammatory and insulin-resistant state. Tumor necrosis factor-alpha (TNF-α) was also elevated (7.6 ± 2.4 pg/mL), further supporting the presence of chronic low-grade inflammation (Table 2).

Evaluation of subclinical atherosclerosis revealed that mean carotid intima-media thickness (CIMT) was 0.84 ± 0.17 mm, with 28% of patients showing values greater than 0.9 mm, suggestive of early atherosclerotic changes. Correlation analysis demonstrated that higher leptin ($r = 0.42$, $p < 0.001$), resistin ($r = 0.39$, $p = 0.002$), and TNF-α ($r = 0.36$, $p = 0.004$) levels were positively associated with CIMT, whereas adiponectin was inversely correlated with CIMT ($r = –0.44$, $p < 0.001$) (Table 3).

Table 3: Correlation of adipokines with carotid intima-media thickness (CIMT)

Biomarker	Correlation coefficient (r)	p-value
Adiponectin	–0.44	<0.001*
Leptin	0.42	<0.001*
Resistin	0.39	0.002*
Visfatin	0.28	0.012*
TNF-α	0.36	0.004*
hs-CRP	0.31	0.008*

*Significant at $p < 0.05$

These results indicate that prediabetic patients in this cohort demonstrated a dysregulated adipokine profile, insulin resistance, and increased inflammatory markers, which were significantly associated with early atherosclerotic changes as reflected by CIMT.

DISCUSSION

The present study demonstrated that prediabetic patients exhibit significant biochemical and physiological alterations characterized by insulin resistance, dyslipidemia, systemic inflammation, and an unfavorable adipokine profile, all of which were strongly associated with early atherosclerotic changes as reflected by carotid intima-media thickness (CIMT). These findings provide valuable insights into the pathophysiological mechanisms linking adipokine dysregulation with insulin resistance and the progression of subclinical atherosclerosis in individuals at risk of developing type 2 diabetes mellitus (T2DM).

Our results revealed reduced adiponectin levels among prediabetic patients, which correlated inversely with CIMT. Adiponectin is widely recognized as a vasculoprotective adipokine that enhances insulin sensitivity, stimulates nitric oxide production, and exerts anti-inflammatory effects. Its deficiency has been associated with endothelial dysfunction and accelerated atherogenesis. Previous studies have also reported that lower adiponectin concentrations predict both the onset of diabetes and cardiovascular events, supporting the concept that adiponectin serves as a protective biomarker against cardiometabolic disease. [11] In contrast, elevated leptin, resistin, and visfatin levels in our cohort were significantly associated with increased CIMT, highlighting their pathogenic role in vascular remodeling and inflammation. Leptin, although primarily a regulator of satiety, promotes oxidative stress, endothelial dysfunction, and smooth muscle proliferation, thereby contributing to plaque formation. [12] Similarly, resistin and visfatin act as pro-inflammatory mediators that activate nuclear factor-kappa B signaling and induce vascular adhesion molecules, thereby accelerating atherosclerosis in insulin-resistant states. [13]

The inflammatory burden in prediabetes was further evidenced by elevated TNF-α and hs-CRP levels, both of which showed positive correlations with CIMT. TNF-α is a key cytokine implicated in insulin resistance through serine phosphorylation of insulin receptor substrate-1, leading to impaired glucose uptake and endothelial dysfunction.[14] Elevated hs-CRP in our study population suggests the presence of systemic low-grade inflammation, which has been identified as an independent risk factor for cardiovascular disease in prediabetic and diabetic patients.[15] This pro-inflammatory state not only accelerates atherosclerosis but also synergizes with dyslipidemia and insulin resistance to increase cardiovascular risk.

The lipid profile of our study participants was consistent with the classic atherogenic dyslipidemia of insulin resistance, characterized by elevated triglycerides, increased LDL-C, and reduced HDL-C. This dyslipidemia triad plays a pivotal role in the initiation and progression of atherosclerosis. Previous epidemiological studies in South Asia have documented similar lipid abnormalities in prediabetic and diabetic patients, reinforcing the importance of early lipid control in high-risk populations. [16] Importantly, our findings align with earlier reports from Pakistani cohorts where central obesity and dyslipidemia were the strongest predictors of cardiometabolic risk in prediabetes. [17]

CIMT measurement in our study provided a robust marker of subclinical atherosclerosis. Approximately one-third of patients demonstrated CIMT values >0.9 mm, consistent with early vascular changes. Studies conducted globally and regionally confirm that increased CIMT in prediabetic and insulin-resistant individuals predicts future cardiovascular events independent of traditional risk factors. [18] Early detection of such vascular alterations, therefore, provides an opportunity for timely interventions aimed at reducing long-term cardiovascular burden.

Taken together, our results support the hypothesis that adipokine dysregulation, systemic inflammation, and insulin resistance form an interlinked pathogenic network that drives early atherosclerotic progression in prediabetes. Identifying these changes before the onset of overt diabetes is crucial, particularly in high-risk populations such as Pakistan, where lifestyle factors, genetic predisposition, and rapid urbanization are contributing to an epidemic of metabolic disorders. [19] Lifestyle modification, weight reduction, and pharmacological interventions targeting insulin resistance and inflammation may thus serve as effective strategies to delay or prevent cardiovascular complications in this vulnerable group. [20]

CONCLUSION

This study demonstrates that prediabetic patients exhibit significant biochemical and physiological alterations, including insulin resistance, dyslipidemia, systemic inflammation, and an unfavorable adipokine profile, which are closely linked to early atherosclerotic progression as measured by carotid intima-media thickness. Reduced adiponectin and elevated levels of leptin, resistin, visfatin, TNF-α, and hs-CRP were strongly associated with vascular changes, underscoring the role of adipokine imbalance in mediating cardiometabolic risk before the onset of overt diabetes. These findings highlight the importance of early identification and monitoring of adipokine-mediated pathways in prediabetic individuals to facilitate timely preventive interventions and reduce the future burden of ischemic heart disease in high-risk populations such as those in Pakistan.

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Research Interests: The primary research interests of the authors lie in the fields of cardiovascular medicine, metabolic disorders, and the role of biochemical and physiological markers in predicting early disease progression. Particular emphasis is placed on understanding the interplay between insulin resistance, adipokines, and subclinical atherosclerosis, with the aim of improving early detection, prevention, and management strategies in high-risk populations such as prediabetic individuals.

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Author Contributions: MZAR and AS conceived and designed the study. SAZ and TM were responsible for patient recruitment and clinical data acquisition. AAC and FA assisted in laboratory analysis and statistical interpretation. MZAR drafted the initial version of the manuscript, while AS and SAZ critically revised it for intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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