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INFLAMMATORY AND ENDOTHELIAL BIOMARKER ALTERATIONS ASSOCIATED WITH VISCERAL ADIPOSITY IN PREDIABETES

Bhaskara Rao Motamarri[1*], Jaya Jain[2], Ashutosh Jain[3]

[1*]Research scholar, Index Medical College Hospital and Research Centre, Malwanchal University, Indore, Madhya Pradesh. India Email ID: bhaskar.motamarri@gmail.com
[2]Associate professor Department of Biochemistry Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh. India. Email ID: jain02jaya@gmail.com
[3]Assistant professor Department of Physiology Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh. India. Email ID: ashutosh.jain@689gmail.com

***Corresponding author:** Bhaskara Rao Motamarri
*Research scholar, Index Medical College Hospital and Research Centre, Malwanchal University, Indore, Madhya Pradesh. India Email ID: bhaskar.motamarri@gmail.com ORCID: https://orcid.org/0009-0008-6584-3152

Abstract

Background: Dysglycemia and elevated cardiometabolic risk are characteristics of prediabetes, and persistent low-grade inflammation and visceral obesity have been identified as major factors in the development of the condition. However, little is known about the connection between visceral fat and systemic inflammatory indicators in prediabetic people, especially in South Asian communities. to examine the relationship between visceral adiposity and inflammatory biomarkers in prediabetic people versus healthy controls, such as vascular cell adhesion molecule-1 (VCAM-1), interleukin-1 (IL-1), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), and intercellular adhesion molecule-1 (ICAM-1).

Methods: There were 192 participants in this cross-sectional study, 96 of whom had prediabetes and 96 of whom were controls who were matched for age and sex. Using bioelectrical impedance analysis, the visceral fat percentage (VF%) was determined. ELISA was used to check for adhesion molecules and cytokines in fasting blood samples. Independent t-tests were used to examine differences between groups, and Pearson's correlation was used to evaluate the relationships between VF% and inflammatory markers.**Results:** When compared to controls, those with prediabetes showed noticeably different inflammatory profiles. While IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1 were significantly raised (all $p < 0.001$) with very high to extremely large effect sizes (Cohen's $d = 1.97–10.88$), TNF-α levels were lower in prediabetes (10.42 ± 1.18 vs. 15.63 ± 1.35 pg/mL, $p < 0.0001$). All inflammatory markers, such as TNF-α ($r = 0.622$), IL-1 ($r = 0.568$), IL-6 ($r = 0.583$), hsCRP ($r = 0.726$), ICAM-1 ($r = 0.709$), and VCAM-1 ($r = 0.591$), showed positive correlations with VF% (all $p < 0.001$).**Conclusions:** In prediabetic people, visceral obesity is closely associated with endothelial activation and systemic inflammation even prior to the development of type 2 diabetes. According to these results, visceral fat is a metabolically active tissue that contributes to vascular and pro-inflammatory alterations. Early measurement of visceral fat and inflammatory biomarkers may enhance risk assessment and preventative measures in prediabetes.

Keywords: Prediabetes, Visceral adiposity, Inflammation, Cytokines, Endothelial dysfunction, Cardiometabolic risk

Introduction

Prediabetes, which is defined by impaired glucose tolerance or impaired fasting glucose, is a metabolic condition that lies in between normoglycemia and type 2 diabetes mellitus (T2DM). In comparison to other ethnic groups, South Asian populations exhibit a disproportionately higher prevalence and earlier onset, affecting about 470 million individuals worldwide [1,2]. Importantly, prediabetes is not a benign condition; rather, it is closely linked to the development of type 2 diabetes, an elevated risk of cardiovascular disease (CVD), and early death [3,4]. Therefore, early detection and prevention depend on an understanding of the molecular mechanisms causing this transformation.

One important factor in determining cardiometabolic risk is visceral obesity. Visceral adipose tissue (VAT), in contrast to subcutaneous fat, is metabolically active and secretes pro-inflammatory cytokines and adipokines that encourage vascular damage, β-cell dysfunction, and insulin resistance [5,6]. VAT is a more sensitive indicator of metabolic risk than BMI alone because central obesity, even at relatively low body mass index (BMI) levels, is highly correlated with dysglycemia in South Asians [7].

One of the main mechanisms connecting visceral obesity with metabolic dysregulation is chronic low-grade inflammation. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are cytokines that alter insulin signaling and increase systemic inflammation [8,9]. High-sensitivity C-reactive protein (hsCRP), a commonly used biomarker of cardiometabolic risk, is also produced in the liver as a result of these cytokines [10]. Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are two adhesion molecules that promote leukocyte adherence and atherogenesis at the vascular level when endothelial cells are activated by inflammation [11,12]. Even prior to the diagnosis of overt diabetes, these mechanisms collectively create a condition that is pro-inflammatory and pro-atherogenic. There is proof that visceral adiposity plays a crucial part in the development of diabetes from prediabetes. Neeland et al. (2012) showed that incident prediabetes and diabetes were independently predicted by excess visceral fat mass and insulin resistance rather than total adiposity [13]. VAT inflammation mediates this relationship, as immune cell infiltration increases TNF-α and interleukins while decreasing insulin-sensitizing adiponectin [14]. The visceral adiposity index was validated as a reliable indicator of prediabetes risk by a recent meta-analysis [15]. Additionally, this cycle has been linked to oxidative stress because hyperglycemia accelerates vascular dysfunction by exacerbating chronic inflammation and impairing insulin production [16].

Recent data from South Asian communities emphasize these risks even more. Kim and Kim (2023) discovered that insulin resistance across all prediabetes subtypes was significantly correlated with CT-measured VAT volume [17], whereas visceral fat cut-off values were suggested by Jadhav et al. (2022) as indicators of prediabetes in Indians [18]. Mehta et al. (2020, 2021) emphasized that South Asians have a disproportionately high burden of diabetes and cardiovascular disease because of their poor body composition and impaired glucose metabolism [19]. According to Gujral et al. (2020), South Asian Americans had a 32% incidence of prediabetes or diabetes within five years, and visceral fat area and hepatic fat attenuation were significant predictors of glycemic progression [20].

The relationship between visceral adiposity, systemic inflammatory cytokines, and endothelial dysfunction in prediabetic people, especially in South Asian cohorts, has not been thoroughly assessed in many research, despite these advancements. Identifying early biomarkers of metabolic and vascular risk and directing specialized preventative measures may be made easier with the clarification of these connections. Thus, the current study sought to determine how visceral adiposity and inflammatory biomarkers (TNF-α, IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1) in prediabetic people differed from those in healthy controls. To ascertain if visceral fat is a major contributor to systemic inflammation and endothelial dysfunction in the prediabetic condition, we integrated biochemical, vascular, and anthropometric indicators.

Materials and Methods

Study Design and Setting

This cross-sectional observational study examined the relationship between visceral adiposity and systemic inflammation in prediabetic people. It was carried out in the Department of Biochemistry, Index Medical College and Research Centre, Indore, Madhya Pradesh, India. Every lab operation was carried out in a biochemistry lab that has earned NABL accreditation and is furnished with high-precision colorimetric analyzers, automated ELISA systems, and standardized anthropometric evaluation instruments. The plan made it possible to gather anthropometric, metabolic, and inflammatory data all at once in a non-interventional environment.

Ethical Approval and Consent

This study's procedure was approved by Index Medical College's Institutional Ethics Committee (IEC) (Ref. MU/Research/EC/Ph.D/2022/353). Ethical protocols adhered to the Indian Council of Medical Research's (ICMR) National Guidelines for Biomedical Research involving Human Participants (2017) and the Declaration of Helsinki (2013 revision). Following a thorough discussion of the study's goals, methods, dangers (such as the discomfort associated with blood drawing), and advantages (such as metabolic health profiling), all participants eventually provided written informed consent. By giving all data anonymized codes and limiting access to the research team alone, confidentiality was guaranteed.

Participant Recruitment and Eligibility

Participants were recruited from outpatient departments and community health camps under institutional public health initiatives. A total of 192 adults (96 prediabetic individuals and 96 age- and sex-matched normoglycemic controls) were enrolled.

Inclusion criteria: According to American Diabetes Association (ADA) guidelines, persons between the ages of 18 and 35 who have prediabetes have fasting plasma glucose (FPG) of 100–125 mg/dL and/or glycated hemoglobin (HbA1c) of 5.7–6.4%.

Exclusion criteria: The presence of acute or chronic inflammatory or autoimmune diseases, cardiovascular issues, endocrine abnormalities, cancers, pregnancy/lactation, or the diagnosis of type 2 diabetes.

Visceral Fat Assessment

Based on bioelectrical impedance analysis (BIA), a validated multi-frequency segmental body composition analyzer (OMRON HBF-701) was used to quantify visceral fat percentage (VF%). Participants fasted throughout the whole night before the test, abstained from coffee and alcohol for 12 hours, and did not exercise for 24 hours in order to reduce variability.

Blood Sample Collection and Biochemical Analysis

Aseptic procedures were used to obtain 8–10 mL of venous blood between 8:00 and 10:00 AM following a 10- to 12-hour overnight fast. EDTA, fluoride, and plain vacutainer containers were used to collect the samples. They were then centrifuged for 10 minutes at 4°C at 3000 rpm, and plasma/serum aliquots were kept at -80°C. To make sure they were stable, all samples were examined within 30 days.

Inflammatory Marker Assays

Enzyme-linked immunosorbent assay (ELISA) kits with verified sensitivity and specificity were used to measure inflammatory markers. High-sensitivity C-reactive protein (hsCRP), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were all present in the panel. Every experiment was carried out twice, and intra-assay coefficients of variation were kept to less than 10%.

Statistical Analysis

For statistical studies, SPSS version 27.0 was used. Standard deviation (SD) ± mean was used to express the data. Independent sample t-tests were used to evaluate between-group comparisons. To

assess the relationships between visceral fat percentage and inflammatory markers in the prediabetic group, Pearson's correlation coefficients were calculated. A statistically significant result was defined as a two-tailed $p < 0.05$.

Result

(TNF-α):

Between the prediabetic and control groups, the mean TNF-α concentrations were 10.42 ± 1.18 pg/mL and 15.63 ± 1.35 pg/mL, respectively. A highly significant difference was found using a two-sample t-test (pooled variance): $t(190) = -30.33$, $p < 0.0001$. Participants with prediabetes had decreased TNF-α levels by -5.21 pg/mL (95% CI: -5.88 to -4.54). The test power was outstanding ($1–\beta = 0.93$), and the effect size was incredibly huge (Cohen's $d = 4.38$), suggesting a significant magnitude of difference. (F-test, $p = 0.87$) The assumption of equal variances was satisfied. In contrast to healthy controls, prediabetic individuals had considerably lower levels of circulating TNF-α, which suggests that inflammatory signaling is changed in the prediabetic state (Figure 1A).

IL-1 (pg/ml)

The prediabetic group's mean IL-1 concentration (5.42 ± 0.68 pg/ml) was substantially greater than that of the controls (3.21 ± 0.54 pg/ml). A highly significant difference was confirmed by a two-sample t-test (pooled variance) with $t(190) = –15.84$ and $p = 0.000141$. Between groups, the mean difference was 2.21 pg/ml (95% CI: –2.76 to –1.66). The statistical power was strong ($1–\beta = 0.93$), and the effect size was quite large (Cohen's $d = 2.29$). But according to the F-test, $p = 0.000000342$, the assumption of equal variances was not satisfied. According to these results, individuals with prediabetes had significantly higher IL-1 levels, which is in line with increased pro-inflammatory activity (Figure 1B).

IL-6 (pg/ml)

In comparison to the control group, the prediabetic group's mean IL-6 concentration was noticeably greater. Using the t distribution (df = 190, two-tailed), a two-sample t-test (pooled variance) revealed a highly significant difference, $t(190) = –13.61$, $p = 0.006642$. The rejection of the null hypothesis (H_0) thus confirmed that there was a difference in the average IL-6 levels between the groups. With a standard error of 0.201, the mean difference was -2.73 pg/ml (95% CI: -3.52 to -1.94). The test power was outstanding ($1–\beta = 0.93$), and the effect size was quite significant (Cohen's $d = 1.97$), suggesting a strong magnitude of difference. There was a breach of the equal variance assumption (F-test, $p = 0.0242$). Overall, IL-6 levels were significantly higher in prediabetic subjects than in controls, indicating increased pro-inflammatory activity (Figure 1C).

hsCRP (mg/L)

In comparison to the control group, the prediabetic group's mean hsCRP concentration was noticeably greater. Using the t distribution (df = 190, two-tailed) and a two-sample t-test (pooled variance), a highly significant difference was found ($t(190) = –53.08$, $p < 0.001$). The null hypothesis (H_0) was thus disproved, indicating that there was a significant difference in the average hsCRP levels between the groups. With a standard error of 0.092, the mean difference was –4.89 mg/L (95% CI: –5.16 to –4.62). The test power was outstanding ($1–\beta = 0.93$), and the effect size was very significant (Cohen's $d = 7.66$), indicating a very substantial magnitude of difference. There was a violation of the premise of equal variances (F-test, $p = 0.0466$). High-sensitivity C-reactive protein (hsCRP) levels were significantly higher in prediabetic subjects overall than in controls, indicating a strong pro-inflammatory condition (Figure 1D).

ICAM-1 (ng/ml)

In comparison to the control group, the prediabetic group's mean ICAM-1 concentration was noticeably greater. Using the t distribution (df = 190, two-tailed) and a two-sample t-test (pooled variance), a highly significant difference was found ($t(190) = -75.35$, $p < 0.001$). The rejection of the null hypothesis (H_0) thus confirmed that there were significant differences in ICAM-1 levels across groups. With a standard error of 2.83, the mean difference was –213.48 ng/ml (95% CI: –224.63 to –

202.33). With a Cohen's d of 10.88, the effect size was incredibly huge, suggesting a significant magnitude of change. Excellent power was shown by the test (1–β = 0.93). However, there was a violation of the premise of equal variances (F-test, $p < 0.001$). ICAM-1 levels were significantly higher in prediabetic patients overall than in controls, indicating strong endothelial activation (Figure 1E).

Serum VCAM-1 Levels

The group with prediabetes had a considerably greater mean VCAM-1 concentration than the control group. The t distribution (df = 190, two-tailed) was used in a two-sample t-test (pooled variance), which revealed a highly significant difference ($t(190) = –25.09$, $p < 0.001$). Thus, it was confirmed that there was a difference in the average VCAM-1 levels across the groups and the null hypothesis (H_0) was rejected. –131.26 ng/ml was the mean difference (95% CI: –151.90 to –110.62), while the standard error was 5.23. There was a significant degree of difference, as indicated by the effect size (Cohen's d = 3.62), and the test power was excellent (1–β = 0.93). According to the F-test, $p = 0.0796$, the premise of equal variances was not broken. Overall, prediabetic subjects' VCAM-1 values were much higher than those of controls, indicating vascular dysfunction and strong endothelial activation (Figure 1E).

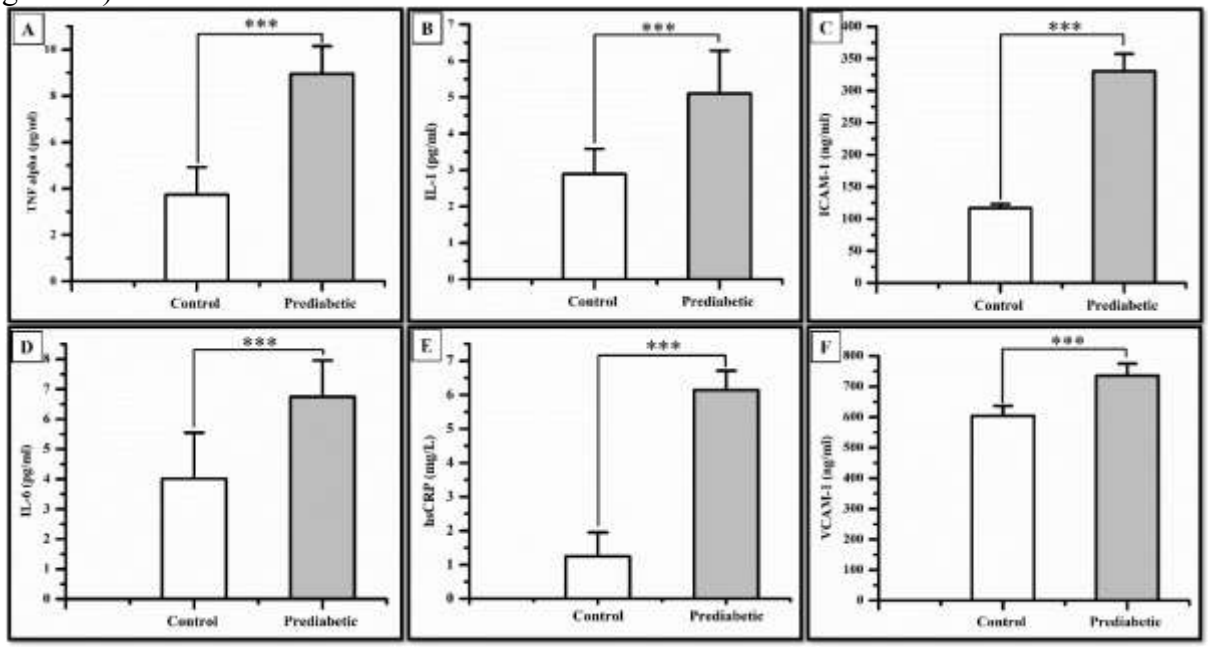

Figure 1. Comparison of inflammatory marker concentrations between prediabetic (n = 96) and control (n = 96) groups. Bar graphs represent mean ± SD values for (A) TNF-α (pg/mL), (B) IL-1 (pg/mL), (C) IL-6 (pg/mL), (D) hsCRP (mg/L), (E) ICAM-1 (ng/mL), and (F) VCAM-1 (ng/mL). Independent two-sample t-tests revealed highly significant group differences for all markers ($p < 0.001$), with prediabetic individuals exhibiting significantly lower TNF-α and markedly higher IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1 concentrations. Error bars represent standard deviations. Statistical significance is indicated by superscripted stars: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; NS = non-significant.

Correlation Between Visceral Fat and Inflammatory Markers in Prediabetic Individuals

In prediabetic individuals, the research showed substantial positive correlations between visceral fat percentage and all assessed inflammatory markers, highlighting the close relationship between systemic inflammation and adiposity.

Visceral fat showed moderate-to-strong correlations with pro-inflammatory cytokines. In particular, there was a strong correlation between elevated visceral adiposity and increased TNF-α secretion, as seen by the TNF-α correlation at $r = 0.622$ ($p < 0.001$) (Figure 2A). Moderate-to-strong associations were also observed for IL-1 ($r = 0.568$, $p < 0.001$) (Figure 1B). and IL-6 ($r = 0.583$, $p < 0.001$) (Figure

1C), indicating that visceral fat functions as an active endocrine tissue that contributes to the release of cytokines and the propagation of low-grade inflammation.

Visceral fat and systemic inflammatory burden, as measured by hsCRP, were most strongly correlated ($r = 0.726$, $p < 0.001$) (Figure 1D). This emphasizes hsCRP's value as a cardiometabolic risk factor in prediabetes by demonstrating that it is a sensitive biomarker that connects central obesity and chronic inflammation.

Additionally, there was a strong correlation between visceral fat and endothelial activation indicators. VCAM-1 had a moderate-to-strong connection ($r = 0.591$, $p < 0.001$) (Figure 1E), whereas ICAM-1 demonstrated a significant correlation ($r = 0.709$, $p < 0.001$) (Figure 1F). These results provide a molecular link between obesity, inflammation, and early atherosclerotic alterations by indicating that visceral fat not only causes systemic inflammation but also contributes to vascular dysfunction.

Collectively, these results emphasize that visceral adiposity in prediabetic individuals is not merely a fat depot but a metabolically active tissue promoting cytokine release, systemic inflammation, and endothelial activation. This inflammatory milieu may accelerate the transition from prediabetes to overt cardiometabolic disease.

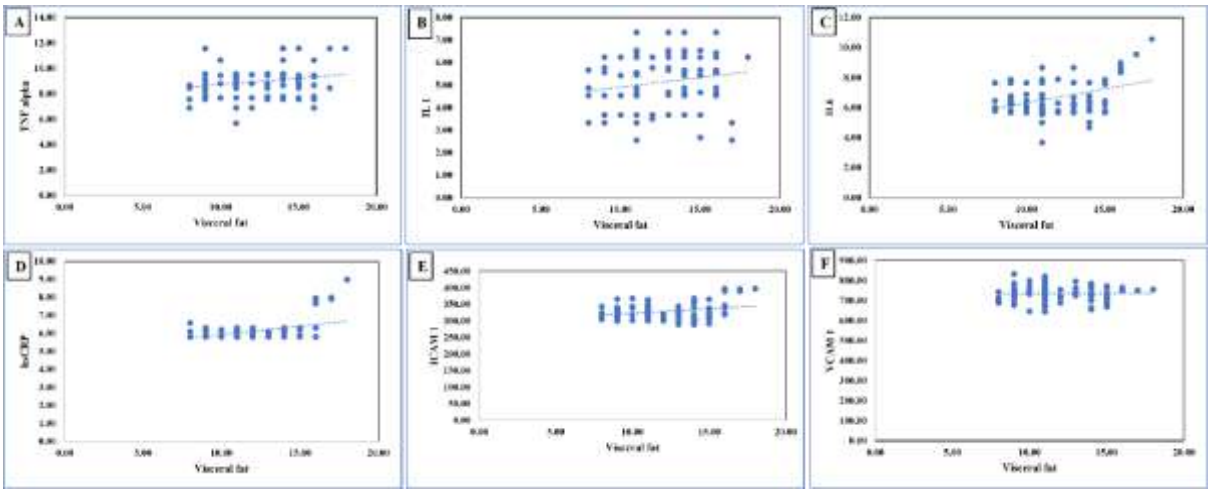

Figure 2. Correlation between visceral fat percentage and inflammatory markers in prediabetic individuals (n = 96). Scatterplots illustrate positive associations between visceral adiposity and (A) TNF-α, (B) IL-1, (C) IL-6, (D) hsCRP, (E) ICAM-1, and (F) VCAM-1, indicating that increased visceral fat is linked with heightened systemic inflammation and endothelial activation.

Discussion

According to this study, visceral obesity in prediabetic people is closely linked to endothelial activation and systemic inflammation. In comparison to the controls, the visceral fat percentages and inflammatory biomarkers, such as IL-1, IL-6, hs-CRP, ICAM-1, and VCAM-1, were considerably greater in the prediabetic patients. These indicators showed strong positive relationships with visceral fat, especially hs-CRP and ICAM-1, indicating that visceral fat is an active endocrine organ that drives vascular and inflammatory dysfunction rather than just being an inert energy store.

Increased levels of IL-1 and IL-6 in prediabetic people are consistent with earlier research showing that these cytokines are key mediators of insulin resistance, β-cell malfunction, and low-grade systemic inflammation [8,21]. The significantly elevated hs-CRP seen in our investigation is consistent with IL-6's role in hepatic acute-phase activation. The strongest correlation was found between visceral fat and hs-CRP, a reliable biomarker of cardiometabolic risk, confirming its function as a clinical link between inflammation, cardiovascular disease, and adiposity [22].

The results for TNF-α were more complex. Although numerous data indicate that obesity and prediabetes are associated with increased TNF-α [23–26], Comparatively lower levels of circulating TNF-α were found in our investigation. This could be the result of compensatory feedback, stage-specific regulation, or local paracrine secretion that is not entirely represented in plasma [27]. Because

of this variability, TNF-α should not be interpreted as a stand-alone biomarker but rather in the context of multi-marker panels.

Individuals with prediabetes had considerably greater levels of ICAM-1 and VCAM-1, which suggests early endothelial dysfunction. Both adhesion molecules promote vascular inflammation and leukocyte adherence, two essential processes in atherogenesis [12]. Their increased prevalence of prediabetes confirms earlier findings that vascular damage starts early and comes before overt diabetes [28,29]. These results imply that cardiovascular risk in this population may be accelerated by the convergence of inflammatory and vascular pathways.

Strong associations between visceral fat and inflammatory markers support the tissue's function as a metabolically active organ that releases adipokines and cytokines, which in turn promote systemic low-grade inflammation [30]. Visceral adipose tissue provides direct portal access to the liver, which enhances its impact on lipid and glucose metabolism in contrast to subcutaneous fat. Compared to Western populations, South Asian people have visceral adiposity and metabolic problems at lower BMI thresholds, making these findings especially pertinent to them [31]. Therefore, using BMI alone may understate the risk of cardiometabolic disease in these populations.

Overall, when the data support the idea that prediabetes is a condition that is already marked by endothelial activation and systemic inflammation rather than being benign. Increased cardiovascular risk and β-cell loss may be caused by elevated IL-1, IL-6, hs-CRP, ICAM-1, and VCAM-1, highlighting the significance of early management. Attenuating these inflammatory pathways and delaying the onset of type 2 diabetes and cardiovascular disease may be possible by reducing visceral adiposity by customized exercise, dietary changes, or anti-inflammatory medications [32].

The study's strengths include its use of direct visceral fat measurement and its focus on a very young South Asian cohort, an underrepresented but high-risk demographic. Its cross-sectional nature, which makes it unable to draw conclusions about causality, its dependence on bioelectrical impedance as opposed to the gold standard of imaging (CT/MRI), and its failure to account for genetic or lifestyle factors are some of its limitations. Moreover, biomarker evaluation was restricted to a select panel, leaving out other important adipokines including adiponectin and leptin.

Future longitudinal research should evaluate the correlation between incident diabetes or cardiovascular disease, inflammatory biomarkers, and visceral obesity over time. It will be crucial to conduct interventional trials aimed at reducing visceral fat to ascertain whether reducing adiposity results in a lower burden of inflammation. Using multi-omics techniques (metabolomics, proteomics, and transcriptomics) may help to elucidate the mechanisms that connect systemic inflammation and visceral adipose tissue. Finally, the creation of biomarker cut-offs and population-specific thresholds for visceral fat may improve risk stratification for South Asians and other high-risk populations.

Conclusion

This study demonstrates that, even prior to the development of overt type 2 diabetes, visceral obesity in prediabetic people is closely associated with endothelial activation and systemic inflammation. Participants with prediabetes showed paradoxically lower levels of circulating TNF-α and considerably higher levels of IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1 when compared to normoglycemic controls. Crucially, there was a significant correlation between the proportion of visceral fat and every biomarker that was tested. This suggests that visceral fat is a metabolically active tissue that contributes to vascular dysfunction and persistent low-grade inflammation.

According to this study, visceral obesity in prediabetic people is closely linked to endothelial activation and systemic inflammation even before overt type 2 diabetes manifests. While circulating TNF-α paradoxically decreased, prediabetic subjects showed significantly higher levels of IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1 than normoglycemic controls. Visceral fat is a metabolically active tissue that contributes to persistent low-grade inflammation and vascular dysfunction. This is shown by the significant positive correlation between visceral fat percentage and all tested biomarkers.

Conclusion

This study demonstrates a substantial correlation between systemic inflammation and endothelial activation and visceral obesity in prediabetic subjects. Participants with prediabetes showed significantly higher levels of IL-1, IL-6, hsCRP, ICAM-1, and VCAM-1, as well as altered TNF-α signaling, as compared to normoglycemic controls. Crucially, the percentage of visceral fat showed a strong and positive correlation with all endothelial and inflammatory indicators, highlighting its function as a metabolically active tissue that promotes vascular dysfunction and low-grade inflammation. These results link central obesity to early vascular damage and chronic inflammation, highlighting visceral adiposity as a major molecular driver in the pathophysiology of prediabetes. Therefore, preventing the progression of prediabetes to overt type 2 diabetes mellitus and cardiovascular disease may require early detection and focused visceral fat reduction.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

References

1 Anjana RM, Deepa M, Pradeepa R, Mahanta J, Narain K, Das HK, et al. Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR–INDIAB population-based cross-sectional study. *Lancet Diabetes Endocrinol.* 2017;5:585–96, https://doi.org/10.1016/S2213-8587(17)30174-2

2 Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012;379:2279–90, https://doi.org/10.1016/S0140-6736(12) 60283-9

3 Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016:i5953, https://doi.org/10.1136/bmj.i5953

4 Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N. Engl. J. Med.* 2018;379:633–44, https://doi.org/10.1056/NEJMoa1800256

5 Després J-P. Body Fat Distribution and Risk of Cardiovascular Disease. *Circulation* 2012;126:1301–13, https://doi.org/10.1161/CIRCULATIONAHA.111.067264

6 Tchernof A, Després J-P. Pathophysiology of Human Visceral Obesity: An Update. *Physiol. Rev.* 2013;93:359–404, https://doi.org/10.1152/physrev.00033.2011

7 Misra A, Khurana L. The Metabolic Syndrome in South Asians: Epidemiology, Determinants, and Prevention. *Metab. Syndr. Relat. Disord.* 2009;7:497–514, https://doi.org/10.1089/ met.2009.0024

8 Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat. Rev. Immunol.* 2011;11:98–107, https://doi.org/10.1038/nri2925

9 Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–7, https://doi.org/10.1038/nature05485

10 Ridker PM. C-Reactive Protein: Eighty Years from Discovery to Emergence as a Major Risk Marker for Cardiovascular Disease. *Clin. Chem.* 2009;55:209–15, https://doi.org/10.1373 /clinchem.2008.119214

11 Hwang S-J, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto AM, et al. Circulating Adhesion Molecules VCAM-1, ICAM-1, and E-selectin in Carotid Atherosclerosis and Incident Coronary Heart Disease Cases. *Circulation* 1997;96:4219–25, https://doi.org/10.1161/ 01.CIR.96.12.4219

12 Libby P, Ridker PM, Maseri A. Inflammation and Atherosclerosis. *Circulation* 2002;105:1135–43, https://doi.org/10.1161/hc0902.104353

13 Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional Adiposity and the Risk of Prediabetes and Type 2 Diabetes in Obese Adults. *JAMA* 2012;308:1150, https://doi.org/10.1001/2012.jama.11132

14 Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of Adipose Tissue

Inflammation to the Development of Type 2 Diabetes Mellitus. Compr. Physiol., Wiley; 2018, p. 1–58, https://doi.org/10.1002/cphy.c170040
15 Wang D, Fang R, Han H, Zhang J, Chen K, Fu X, et al. Association between visceral adiposity index and risk of prediabetes: A meta-analysis of observational studies. *J. Diabetes Investig.* 2022;13:543–51, https://doi.org/10.1111/jdi.13685
16 Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. *J. Physiol. \& Pharmacol.* 2019;70, https://doi.org/https://doi.org/10.26402/jpp.2019.6.01
17 Kim J, Kim K. CT-based measurement of visceral adipose tissue volume as a reliable tool for assessing metabolic risk factors in prediabetes across subtypes. *Sci. Rep.* 2023;13:17902, https://doi.org/10.1038/s41598-023-45100-8
18 Jadhav RA, Maiya GA, Shivashankara KN, Umakanth S. Measurement of visceral fat for early prediction of prediabetes—Cross-sectional study from Southern India. *J. Taibah Univ. Med. Sci.* 2022;17:983–90, https://doi.org/10.1016/j.jtumed.2022.05.006
19 Mehta A, Singh S, Saeed A, Mahtta D, Bittner VA, Sperling LS, et al. Pathophysiological Mechanisms Underlying Excess Risk for Diabetes and Cardiovascular Disease in South Asians: The Perfect Storm. *Curr. Diabetes Rev.* 2021;17, https://doi.org/10.2174/1573399816666200703182458
20 Gujral UP, Narayan KMV, Kandula NR, Liu K, Kanaya AM. Incidence of diabetes and prediabetes and predictors of glycemic change among South Asians in the USA: the MASALA study. *BMJ Open Diabetes Res. Care* 2020;8:e001063, https://doi.org/10.1136/bmjdrc-2019-001063
21 Pickup JC. Inflammation and Activated Innate Immunity in the Pathogenesis of Type 2 Diabetes. *Diabetes Care* 2004;27:813–23, https://doi.org/10.2337/diacare.27.3.813
22 Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. *Eur. Heart J.* 2020;41:2952–61, https://doi.org/10.1093/eurheartj/ehaa160
23 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose Expression of Tumor Necrosis Factor-α: Direct Role in Obesity-Linked Insulin Resistance. *Science (80-.).* 1993;259:87–91, https://doi.org/10.1126/science.7678183
24 Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am. J. Physiol. Metab.* 2001;280:E745–51, https://doi.org/10.1152/ajpendo.2001.280.5.E745
25 Marinkovic D, Dragovic T, Stanojevic I, Djuric P, Dejanovic B, Rakocevic J, et al. Low-grade inflammation and inflammatory mediators in individuals with prediabetes. *Vojnosanit. Pregl.* 2024;81:547–54, https://doi.org/10.2298/VSP240328056M
26 Rai PS, Shivarajashankara YM, Bhandary RB, Prajna RH, Shetty S, Bhandary YP. Targeting Inflammatory Pathways in Type 2 Diabetes: A Focus on Adiponectin, Tumour Necrosis Factor-alpha and Interleukin-6 for Potential Therapeutic Interventions. *Adv. Hum. Biol.* 2025, https://doi.org/10.4103/aihb.aihb_61_25
27 Sethi JK, Hotamisligil GS. Metabolic Messengers: tumour necrosis factor. *Nat. Metab.* 2021;3:1302–12, https://doi.org/10.1038/s42255-021-00470-z
28 Meigs JB. Biomarkers of Endothelial Dysfunction and Risk of Type 2 Diabetes Mellitus. *JAMA* 2004;291:1978, https://doi.org/10.1001/jama.291.16.1978
29 Abdullah RA, Abdulrahman IS. Circulating Cell Adhesion Molecules Level in Type 2 Diabetes Mellitus and Its Correlation with Glycemic Control and Metabolic Syndrome: A Case-control Study. *Med. J. Babylon* 2023;20:64–70, https://doi.org/10.4103/MJBL.MJBL_246_22
30 Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral Fat Adipokine Secretion Is Associated With Systemic Inflammation in Obese Humans. *Diabetes* 2007;56:1010–3, https://doi.org/10.2337/db06-1656

31 Jung SH, Ha KH, Kim DJ. Visceral Fat Mass Has Stronger Associations with Diabetes and Prediabetes than Other Anthropometric Obesity Indicators among Korean Adults. *Yonsei Med. J.* 2016;57:674, https://doi.org/10.3349/ymj.2016.57.3.674

32 Jadhav RA, Maiya GA, Umakanth S, Shivashankara KN. Effect of a Customized Physical Activity Promotion Program on Visceral Fat and Glycemic Parameters in Individuals With Prediabetes: A Randomized Controlled Trial. *J. Phys. Act. Heal.* 2024;21:164–70, https://doi.org/10.1123/jpah.2023-0486