Journal of Associated Medical Sciences 2026; 59(2): 298-306

JAMS Journal of Associated Medical Sciences

Scopus Indexed & Thai-Journal Citation Index Centre (TCI)

Journal of Associated Medical Sciences

Journal homepage: https://www.tci-thaijo.org/index.php/bulletinAMS/index

Comparison of carotid intima media thickness and high sensitive c-reactive protein with hemostasis model assessment for insulin resistance in prediabetes and normoglycemic patients: A case-control study

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ARTICLE INFO

Article history:
Received 11 October 2025
Accepted as revised 16 February 2026
Available online 16 March 2026

Keywords:
Insulin resistant, carotid artery, diabetes

ABSTRACT

Background: Hyperglycaemia and insulin resistance (IR) are two significant risk factors for atherosclerotic cardiovascular disease (ASCVD). While the relationship between diabetes and atherosclerosis has been extensively studied and well established, data on prediabetes are scarce. The carotid artery intima-media thickness (CIMT) and high-sensitivity C-reactive protein (hs-CRP) are both well-established markers of subclinical atherosclerosis.

Objectives: The purpose of this study was to compare homeostasis model assessment-IR (HOMA-IR) levels in prediabetic and normoglycemic subjects, as well as to assess the relationship between HOMA-IR with hs-CRP and CIMT levels between these two groups.

Materials and methods: This case-control study enrolled 52 prediabetic patients and 52 normoglycemic controls. Glycaemic profile and hs-CRP were determined and HOMA-IR were calculated using fasting glucose and insulin values and bilateral CIMT measurements were taken. SPSS (ver_24.0) was used for analysis and based on the distribution of data analysis was performed.

Results: In both cases and controls, the mean serum fasting insulin level was 13.92±4.27 mIU/mL and 5.21±2.46 mIU/mL, respectively (p<0.001). The mean HOMA-IR values were 3.70±1.1 and 1.21±0.58, respectively (p<0.001). The mean CIMT was significantly greater in prediabetics (0.62±0.07mm) than in controls (0.45±0.08 mm) (p<0.001). Additionally, prediabetics had significantly higher serum-levels (5.70±3.35 mg/L) tan controls (1.88±1.35 mg/L) (p<0.001). A positive correlation of HOMA-IR existed between mean CIMT (p<0.001; r=0.631), and hs-CRP (p<0.001; r=0.498).

Conclusion: Prediabetic adults had higher CIMT and hs-CRP than normoglycemic controls, and HOMA-IR correlated positively with both, indicating greater subclinical atherosclerosis burden. These associations suggest IR may aid ASCVD risk stratification in prediabetes, though longitudinal studies are needed to confirm prognostic value.

Introduction

Noncommunicable diseases-especially athero-sclerotic cardiovascular disease (ASCVD)-remain the leading global cause of death, and diabetes is a major accelerator of this risk. The latest International Diabetes Federation (IDF) estimates indicate a rapidly rising burden of diabetes worldwide, with substantial

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doi: 10.66285/JAMS.2026.061
E-ISSN: 2539-6056

mortality and health-care costs.[1,2]

Prediabetes, defined by the American Diabetes Association (ADA) as impaired fasting glucose (IFG) 100-125 mg/dL, 2-hr oral glucose tolerance test (OGTT) 140-199 mg/dL, or HbA1c 5.7-6.4%, is common and clinically important because it signals elevated cardiometabolic risk.[3] Large meta-analyses show that prediabetes is associated with higher all-cause mortality and cardiovascular events compared with normoglycemia.[4] The risk of developing microvascular and macrovascular consequences, including nephropathy, retinopathy, peripheral neuropathy, cardiovascular events, and stroke emerge earlier in the transition from normal glucose to overt diabetes among these patients.[5]

IFG and impaired glucose tolerance (IGT) are two types of prediabetes that occur early in the spectrum of diabetes and have an estimated Relative Risk (RR) for ASCVD of 0.97 to 1.30 for IGT and 1.12 to 1.37 for IFG.[6-8] The risk associated with IFG and IGT is not well-established, despite a continuum of risk that extends into and below the pre-diabetic glucose range.

Subclinical atherosclerosis can be quantified noninvasively by carotid intima-media thickness (CIMT) using B-mode ultrasound, which correlates with traditional risk factors and future cardiovascular events. Contemporary reviews note standardized acquisition (segment proximal to the bifurcation, far-wall measurement, averaging multiple cardiac cycles) and support CIMT as an early marker of vascular injury.[9-11]

Age-stratified analyses also suggest CIMT improves prediction of cardiovascular death beyond traditional risk factors in adults <55 years.[12] Moreover, CIMT also corresponds strongly with ASCVD risk variables such blood pressure, lipid profiles, and smoking, as well as the severity of coronary artery disease (CAD) in both men and women.[13]

Inflammation is integral to dysglycemia-related atherogenesis. Systemic inflammation contributes to atherosclerosis, where high-sensitivity C-reactive protein (hs-CRP) is a practical inflammatory biomarker that tracks cardiometabolic risk.[14] Prospective data and meta-analyses in the cardiometabolic cohorts, link higher hs-CRP with incident type 2 diabetes mellitus (T2DM) and adverse cardiovascular outcomes across populations.[15-17] The hs-CRP levels also corresponded with the stage of insulin resistance and beta-cell dysfunction.[15] Findings from Indian cohorts further connect metabolic risk profiles with vascular changes relevant to CIMT.[18,19] In recent years, hs-CRP had emerged as a reliable test measure for predicting cardiovascular risk.

Insulin resistance (IR), commonly estimated by homeostasis model assessment (HOMA-IR), is mechanistically linked to endothelial dysfunction and atherosclerosis. Population data show positive associations between HOMA-IR and CIMT in non-diabetic adults after multivariable adjustment,[20] and contemporary work continues to relate cardiometabolic indices to carotid atherosclerosis burden.

The primary objective of this present study was to compare CIMT and hs-CRP levels between adults with prediabetes and normoglycemic controls, and the secondary objective were to evaluate IR using the HOMA-IR and to examine the associations of HOMA-IR with CIMT and hs-CRP within the study population.

Materials and methods

Study design and setting

A case-control study comparing adults with prediabetes with normoglycemic controls conducted in the Department of General Medicine, at a single tertiary care centre, Pondicherry, India. Methods and reporting followed STROBE recommendations.[21] The study was conducted over a period of 18 months, from January 2020 to June 2021. Ethical approval was obtained from Institutional Human Ethics Committee and informed consent obtained from the patients.

Study participants and definitions

Prediabetes was defined as per ADA criteria,[3] as FPG: 100-125 mg/dL; 2-hr PPG 140-199 mg/dL; or HbA_{1C} 5.7-6.4%. Controls were normoglycemic (FPG levels of 70-99 mg/dl, PPG levels <140 mg/dl, and $HbA1_c$ values <5.7%) by the same standards.

Patients with established history of diabetes (FPG>126mg/dl, 2-hr PPG>200mg/dl, or HbA1c>6.5%), and those with low FPG (<70 mg/dl) or currently on anti-diabetic therapy, individuals with were excluded. Additionally, participants diagnosed with other non-communicable diseases or undergoing treatment for hypertension, dyslipidaemia, or any condition that could influence CIMT were not included in the study.

Sample size and sampling technique

The sample size was estimated using CIMT as the primary variable, based on the findings of Chauhan *et al*.,[8] where the mean CIMT among prediabetic individuals was reported as 0.59±0.11 mm. The required sample size to estimate the mean CIMT with 95% confidence and an absolute precision (d) of 0.03mm was calculated using the formula; (It yields N~52. With a 1:1 case-control design, 52 prediabetes cases and 52 normoglycemic controls were included. A convenience sampling technique was employed to select participants.

Clinical and laboratory measurements

The participants' FPG, PPG, and HbA_{1c} levels were then determined after an overnight fast (8 hours), venous blood was collected in EDTA containers using an automated biochemical analyser. After two hours of 75 gm glucose consumption, blood samples were collected for PPG. The hs-CRP was measured using a validated high-sensitivity immunoassay and reported in mg/L.

HOMA-IR was used to estimate the IR as [fasting insulin (µIU/mL)*fasting glucose (mg/dL)]/405. CIMT was measured by B-mode ultrasound using a 7.5-10 MHz linear-array transducer with participant in the supine position and the head rotated contralaterally. CIMT was measured in the distal common carotid artery (CCA) on both sides, using a 10-mm (1-cm) plaque-free arterial segment located approximately 1cm proximal to the carotid bulb/bifurcation. Measurement was obtained from the far wall (leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface), as recommended in standardised CIMT acquisition protocols. For each side, three end-diastolic measurements (at adjacent points within the selected 10-mm segment) were recorded and averaged to obtain a mean CIMT for that side. The overall mean CIMT was used for the analysis was calculated as the average of the right and left mean CIMT values. Protocol elements followed ASE consensus and recent reviews.[22]

Quality assurance

CIMT measurements were performed by a trained sonographer who was blinded to the participant's glycaemic status. All scans were obtained using a standardized acquisition protocol to minimize measurement variability. To assess the measurement repeatability, CIMT was re-measured in a randomly selected subset of participants on other periods by the same operator, blinded by the initial readings.

Outcomes

Primary outcome was the difference in mean CIMT and hs-CRP between prediabetes and controls, while the secondary outcomes show the association of HOMA-IR with CIMT and hs-CRP.

Statistical analysis

Analyses were performed using SPSS (ver_21.0). Categorical data (frequency (percentage)) and continuous variables (mean±SD and median (IQR)) based on the normality were provided. The Kolmogorov-Smirnov test was used to determine whether the data were normal. Non-parametric tests were performed if normality was refused. When the data sets weren't normally distributed, we used independent t-tests/Mann-Whitney tests to compare quantitative variables between the two groups. The Chi-square test/Fisher's-Exact test was used to examine the relationship between qualitative variables. The correlation coefficient of Spearman rank was utilised to determine the relationship between various factors. The cause-and-effect link between several characteristics was discovered using univariate linear regression. The $p<0.05$ were considered statistically significant.

Results

Among the study population 104 participants, (52 prediabetes; 52 normoglycemic). Mean age was higher in prediabetes (49.77±7.94 years) than controls (45.10±10.70 years), mean difference 4.67 (95% CI 1.01-8.33; p=0.013). Sex distribution: 36 (69.2%)/16 (30.2%) (M/F) in prediabetes and 32 (61.5%)/20 (38.5%) (M/F) in controls. Baseline characteristics of the study participants were presented in Table 1. Glycemia and insulin measures between both groups were presented in Table 2.

Table 1. Baseline characteristics of the study participant.

Variables	Prediabetes** (N=52)	Normoglycemic** (N=52)	Mean differences (95% CI)	*p* value
BMI (kg/m^2)	25.87±5.02	24.88±2.69	0.98 (-0.58 to 2.5)	0.218
SBP (mmHg)	124.15±9.55	120.21±9.79	3.94 (0.179 to 7.705)	0.04*
DBP (mmHg)	81.15±5.4	77.56±7.86	3.59 (0.970 to 6.223)	0.08

Note: **Independent t-test at p<0.05 were statistically significant, **mean±SD, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, CI: confidence interval.*

Table 2. Glycemia and insulin measures among the study participants.

Variables	Prediabetes** (N=52)	Normoglycemia** (N=52)	Mean differences (95% CI)	*p* value
FBG (mg/dL)	107.69±7.31	92.32±8.26	15.32 (12.21-18.36)	<0.001*
PPBG (mg/dL)	157.92±23.71	114.87±21.42	43.05 (34.26-51.85)	<0.001*
HbA_{1C}	6.04±0.00	5.08±0.09	0.97 (0.837-1.163)	<0.001*
FI (mIU/mL)	13.92±4.27	5.21±2.46	8.71 (7.35-10.06)	<0.001*
HOMA-IR	3.70±1.10	1.21±0.58	2.38 (2.01-2.75)	<0.001*

Note: **Independent t-test at p<0.05 were statistically significant, **mean±SD, FBG: fasting blood glucose, PPBG: post-prandial blood glucose,* HbA_{1C}*: glycated hemoglobin, FI: fasting insulin, HOMA-IR: homeostasis model assessment insulin resistance, CI: confidence interval.*

Distribution of hs-CRP among the study participants were presented in Table 3. The mean hs-CRP (mg/L) among the prediabetes patients was 5.70±3.35 mg/L and the normoglycemic patients was 1.88±1.35 mg/L with the mean difference of 3.82 and were statistically significant (95% CI: 2.83-4.81; *p*<0.00). Similarly, the mean CIMT (mm) was 0.62±0.07 mm and 0.45±0.08 mm among the prediabetes and normoglycemic patients, respectively and were statistically significant with the mean difference of 0.16 (95% CI: 0.13- 0.21; *p*<0.001).

Table 3. hs-CRP levels among the study participants

hs-CRP (mg/L)	Prediabetes (N=52) N (%)	Normoglycemia (N=52) N (%)	Total	*p* value
<1	0 (0.0)	16 (30.8)	16 (15.3)	<0.001*
1-2.99	9 (17.3)	31 (59.6)	45 (43.2)	<0.001*
3-9.99	34 (65.4)	5 (9.6)	39 (37.5)	<0.001*
>10	9 (17.3)	0 (0.0)	9 (8.6)	<0.001*

Note: **Chi-square test, p<0.05 were statistically significant, hs-CRP: high sensitive C-reactive protein.*

Correlation was performed between the HOMA-IR with hs-CRP and CIMT showed positive correlation with both among pre-diabetes patients. For CIMT it showed stronger and positive correlation (r=0.631; *p*<0.001), while with hs-CRP it had moderate correlation (r=0.498; *p*<0.001) and both were statistically significant (Figure 1 and Figure 2).

Moreover, correlation between hs-CRP and CIMT in prediabetes study group were performed where the Pearson correlation coefficient was 0.786, indicating that the strong positive correlation between hs-CRP and CIMT among the prediabetes patient. The correlation was found to be statistically significant (*p*<0.001) (Figure 3).

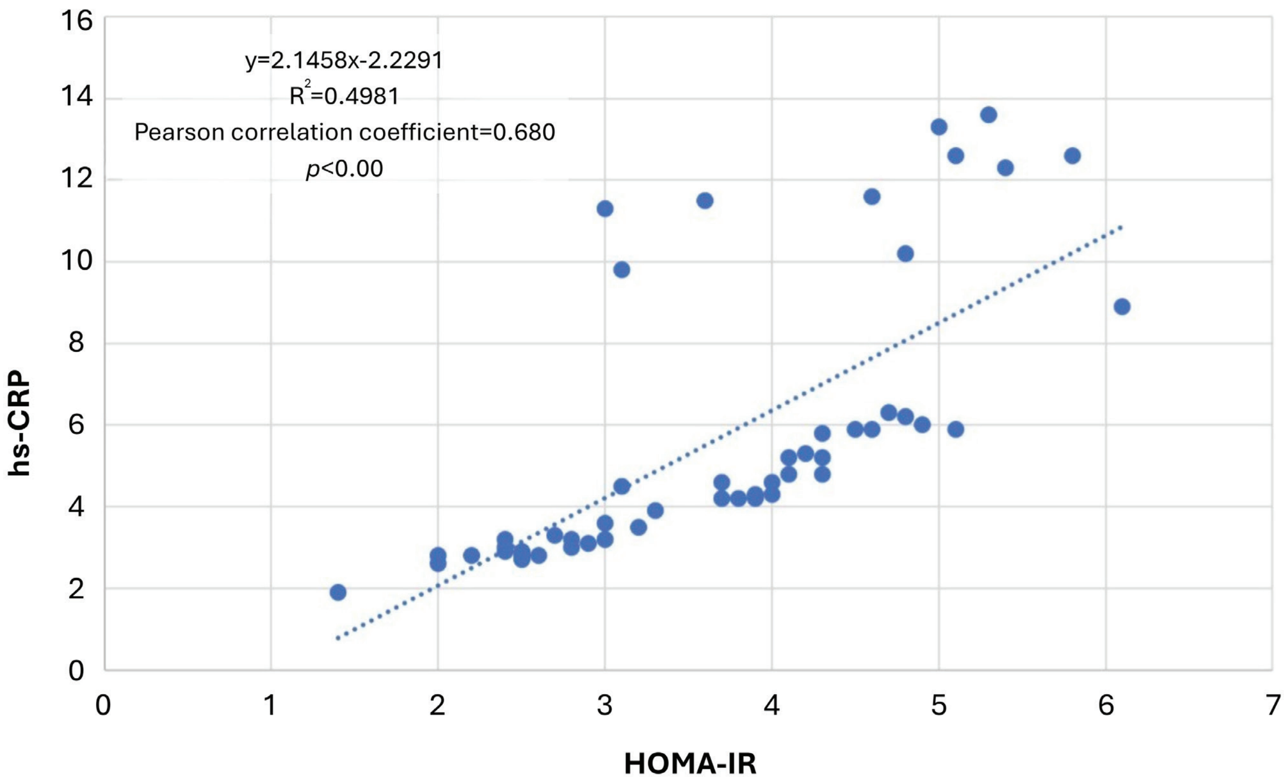

Figure 1. *Association between insulin resistance and CIMT in prediabetes. Scatter plot showing the relationship between HOMA-IR and mean carotid intima-media thickness (CIMT, mm) among adults with prediabetes (N=52). Each point represents one participant. Correlation coefficient (r)=0.631; p<0.001.*

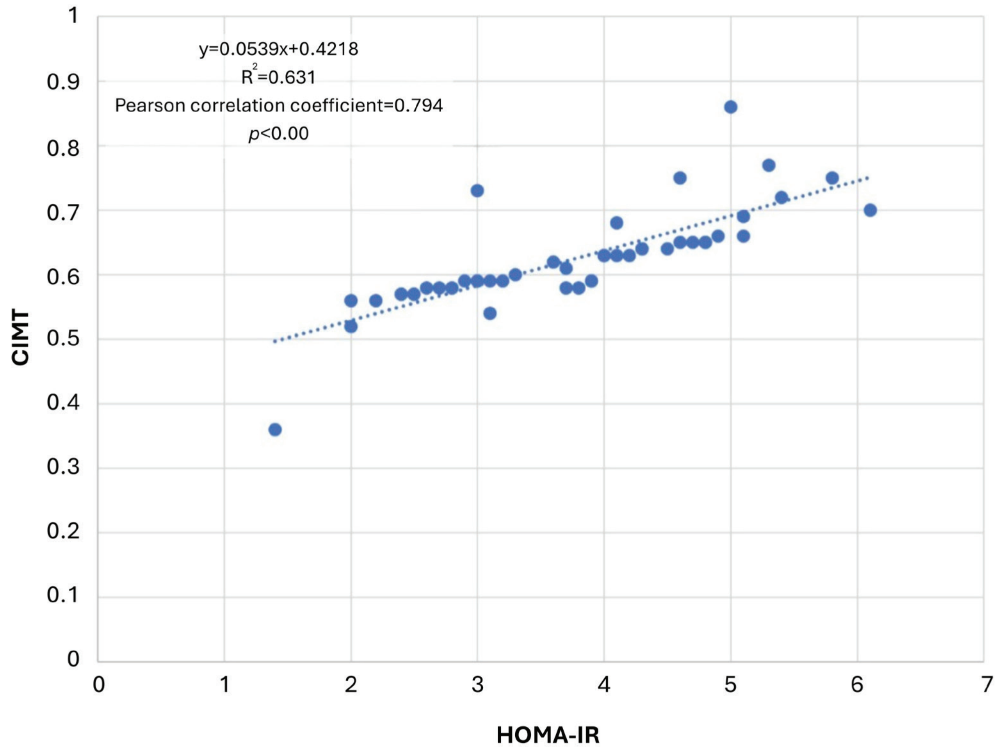

Figure 2. *Association between insulin resistance and hs-CRP in prediabetes. Scatter plot showing the relationship between HOMA-IR and high-sensitivity C-reactive protein (hs-CRP, mg/L) among adults with prediabetes (N=52). Each point represents one participant. Correlation coefficient (r)=0.498; p<0.001.*

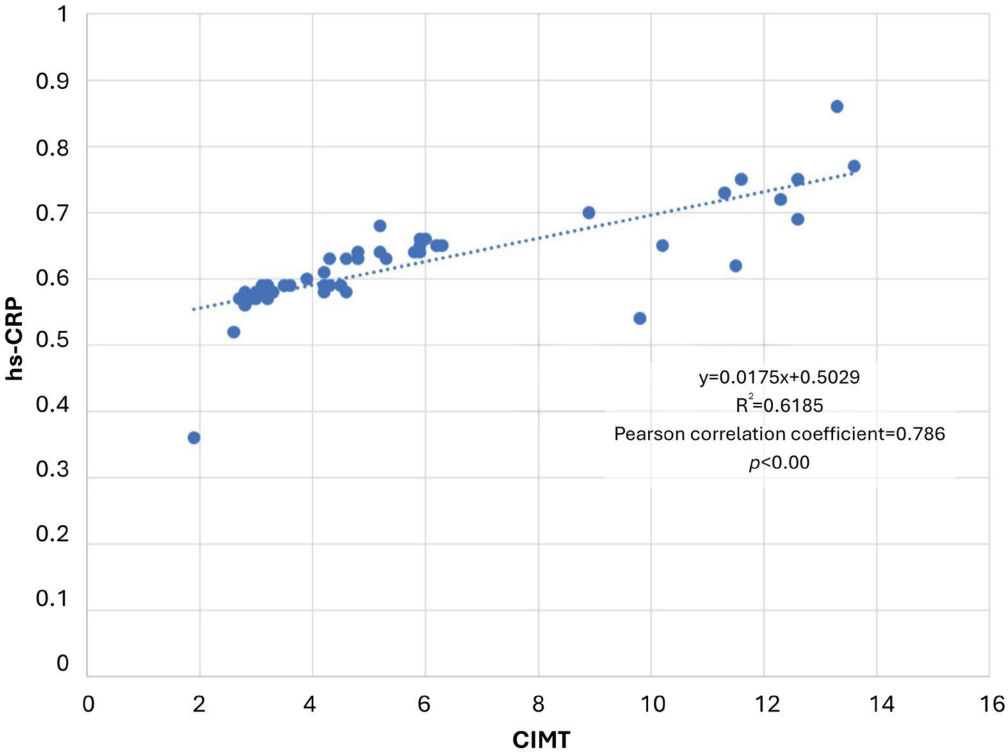

Figure 3. *Association between inflammation and CIMT in prediabetes. Scatter plot showing the relationship between hs-CRP (mg/L) and mean CIMT (mm) among adults with prediabetes (N=52). Each point represents one participant. Correlation coefficient (r)=0.786; p<0.001.*

Discussion

In this case-control study, adults with prediabetes showed higher subclinical atherosclerosis and inflammation than normoglycemic controls. IR correlated positively with both CIMT (r=0.631) and hs-CRP (r=0.498). Various studies have proven that cardiovascular secondary to atherosclerosis is more in diabetics when compared to non-diabetics. But not many studies have been done to prove the associated increase in risk of atherosclerotic cardiovascular disease in prediabetic stage.

An important contribution of this present work is that it provides contemporary data from an Indian tertiary-care setting on the combined assessment of subclinical atherosclerosis (CIMT) and systemic inflammation (hs-CRP) in adults with prediabetes compared with normoglycemic controls. While prior literatures,[4,6,7,9,10,12,13,15,17] established higher cardiovascular risk in overt diabetes, evidence specifically characterising early vascular change and inflammation in the prediabetic stage remains relatively limited, particularly across diverse Indian populations. By demonstrating higher CIMT and hs-CRP in prediabetes and their positive associations with HOMA-IR, our findings add population-relevant support to the concept that atherogenic remodelling and low-grade inflammation begin before clinically overt diabetes.

Prediabetes involves widespread insulin resistance, which disrupts nitric oxide signalling in blood vessels, increases oxidative stress, and speeds up changes in artery walls-all factors that lead to higher CIMT. Additionally, mild inflammation caused by cytokines from fat and the liver (such as IL-6) triggers the liver to produce CRP; elevated hs-CRP levels reflect this inflammatory state and are associated with vascular insulin resistance.[23] Contemporary reviews position CIMT as a validated marker of subclinical atherosclerosis and future ASCVD risk, consistent with our findings.[10,22,24,25] Lower inflammatory burden relates to glycaemic improvement, as cohorts show that lower hs-CRP is associated with regression from prediabetes to normoglycemia.[26] In Mahat et al it has shown that prediabetic subjects have abnormalities in atherogenic indices and CIMT, indicating a higher predilection for the development of cardiovascular disease. As a result, atherogenic indices, in addition to routine lipid parameters, can be used to better assess subclinical atherosclerosis in prediabetic subjects.[27] In Groop *et al*., it was shown that the underlying pathogenesis for IR in overt diabetes and prediabetes was microvascular complications that are secondary to diabetes.[28]

Our mean CIMT difference (0.62 vs 0.45 mm) aligns with multiple reports showing thicker carotid walls in prediabetes. In a 100-case/100-control study, Bhinder *et al*., reported CIMT 0.79±0.06 mm (prediabetes) vs 0.72±0.02 mm (controls) ($p<0.05$).[29] A larger cross-sectional series also found higher common and internal CIMT across impaired glucose states compared with normal metabolism.[30] A recent review summarizes that many-but not all-studies show greater CIMT in prediabetes, noting heterogeneity by measurement segment and population.[31] Earlier comparative data likewise showed higher CIMT in prediabetes vs controls.[32] Together, these support our observation of thicker CIMT in prediabetes.

We observed markedly higher hs-CRP in prediabetes (5.70±3.35 mg/L) than controls (1.88±1.35 mg/L). Population and clinic-based data similarly demonstrate higher hs-CRP with dysglycemia: Ghule *et al*., reported hs-CRP 2.17±0.72 mg/L in prediabetes vs 0.66±0.22 mg/L in controls ($p<0.0001$).[33] In an Indian cohort, median hs-CRP was higher in IFG/IGT (≈2.2-2.3 mg/L) vs NGT (1.64 mg/L).[34] More recently, NHANES analyses show the hs-CRP/HDL-C ratio rises across normal→prediabetes→diabetes and independently associates with prediabetes odds (OR per unit ≈1.13).[35] In Sabanayagam C *et al,* the study that was done in two Asian population has discovered the association between prediabetes and elevated hs-CRP levels.[36] In the study of Pfützner *et al*.'s, relation between hs-CRP and cardiovascular risk has shown that the risk exponentially rises in diabetics and also in prediabetes compared to non-diabetes.[37] These data corroborate our observation that inflammation is higher in prediabetes.

Chauhan et al. has studies between prediabetes and non-diabetes groups and measured CIMT and its correlation with HOMA-IR and hs-CRP.[8] It has proven to show positive correlation between all three parameters. Huang *et al*. has shown that when prediabetes was defined using IFG-ADA, IFG-WHO, IGT, and HbA_{1c}, studies show that it was associated with an increased risk of all-cause mortality, composite cardiovascular events, coronary heart disease, and stroke.[38]

Clinical implications

CIMT and hs-CRP, when interpreted alongside standard risk factors, can help flag higher ASCVD risk among adults with prediabetes. Elevated CIMT reflects early arterial remodelling, while higher hs-CRP signals active low-grade inflammation; together with HOMA-IR they identify a subgroup with greater subclinical burden and may prompt earlier lifestyle and cardiometabolic risk management (e.g., weight reduction, BP/lipid control). Although not diagnostic, CIMT progression relates to future events, supporting its role as an adjunct risk marker in preventive care.[39,40]

Limitations

First, the case-control, single-center design limits causal inference and generalizability. Second, modest sample size (N=104) and partial age imbalance may introduce residual confounding; multivariable adjustment beyond age/sex/BMI (e.g., smoking, lipids, medications) was not fully reported. Third, hs-CRP can be influenced by intercurrent inflammation; although major illnesses were excluded, single-timepoint measurements may misclassify chronic inflammatory status. Finally, CIMT methodology (e.g., segment/side averaging, blinding, reproducibility metrics) should be standardized in future work to enhance comparability.

Conclusion

Adults with prediabetes demonstrated higher CIMT and hs-CRP compared with normoglycemic controls, and HOMA-IR showed positive associations with both CIMT and hs-CRP. These findings support the concept that subclinical atherosclerosis and low-grade inflammation may begin early in the dysglycemic continuum, before overt diabetes. Larger, well-designed prospective studies are needed to confirm these relationships after adjustment for cardiovascular risk factors and to determine whether CIMT and hs-CRP improve risk stratification and predict future cardiovascular events in prediabetes.

Ethical approval

Ethical clearance was obtained from the Institutional Human Ethics Committee (MGMCRI/Res/01/2019/45/IHEC/119).

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

R Prasanna Venkatesh: conceptualization, methodology, writing: review and edit; **Vignessh Raveekumara**: methodology, data analysis; **Kamani Bharath Teja**: data curation, data analysis, writing: original draft.

Acknowledgements

I sincerely acknowledge the staff nurses and laboratory technicians who helped me throughout the study.

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