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Original Research Article

Elevated inflammatory markers in pre-diabetic individuals: correlation with hs-CRP & implications for cardiovascular disease prevention

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Abstract

Background: Pre-diabetes is a condition characterized by elevated blood glucose levels that fall below the diagnostic thresholds for diabetes. It is a precursor to Type 2 diabetes and is associated with an increased risk of cardiovascular diseases (CVD) due to systemic inflammation. Inflammatory markers such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) are known to play critical roles in the progression of insulin resistance and subsequent disease development.

Aim & Objective: To evaluate the association of inflammatory markers, including TNF-α, IL-6, and hs-CRP, with insulin resistance in pre-diabetic individuals compared to normoglycemic controls.

Materials and Methods: This study involved 60 pre-diabetic individuals and a normoglycemic control group. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Serum levels of TNF-α, IL-6, and hs-CRP were measured to evaluate systemic inflammation. Statistical analysis was conducted to determine the correlation between HOMA-IR and inflammatory markers, as well as the interrelationships among the markers.

Results: The study found a strong positive correlation between HOMA-IR and TNF-α (r = 0.925), as well as HOMA-IR and IL-6 (r = 0.766). A significant relationship was also observed between TNF-α and hs-CRP (r = 0.831), highlighting elevated systemic inflammation in pre-diabetic individuals.

Conclusion: The findings indicate that systemic inflammation plays a critical role in the progression of pre-diabetes to Type 2 diabetes and CVD. Inflammatory markers such as TNF-α, IL-6, and hs-CRP can serve as early indicators of disease progression. Early detection and targeted interventions focused on reducing inflammation may help prevent the transition from pre-diabetes to diabetes and mitigate cardiovascular risks, thereby improving patient outcomes.

Keywords: Pre-diabetes, TNF-α, Type 2 Diabetes.

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1. Introduction

Pre-diabetes is diagnosed through two key metrics: Impaired Fasting Glycemia (IFG), reflecting elevated fasting blood glucose levels, and Impaired Glucose Tolerance (IGT), marked by postprandial glucose levels higher than normal. Glycated hemoglobin (HbA1C) values ranging between 5.7% and 6.4% also indicate pre-diabetes.[1] According to the World Health Organization (WHO), IFG is defined by fasting plasma glucose levels between 6.1 and 6.9 mmol/L (110–125 mg/dL),[2] whereas the American Diabetes Association (ADA) updated its definition in 2003 to include fasting plasma glucose levels of 5.6 to 6.9 mmol/L (100–125 mg/dL).[3] Both organizations agree that IGT involves two-hour glucose levels of 7.8 to 11.0 mmol/L (140–199 mg/dL) after a 75-g oral glucose tolerance test.[4]

Individuals with pre-diabetes face a heightened risk of Type 2 diabetes and related complications. Risk factors include advanced age (>45 years), family history of diabetes, prior gestational diabetes, or delivering a high birth weight baby (>4 kg or 9 lbs), along with certain ethnicities and conditions like Polycystic Ovary Syndrome (PCOS) and Acanthosis Nigricans. Other markers include elevated triglycerides (>200 mg/dL), low HDL (<35 mg/dL), high BMI (>25), hypertension (>135/85 mmHg), and chronic low-grade inflammation indicated by elevated cytokines such as IL-1, IL-6, and TNF-α.[5,6] Obesity-related systemic

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inflammation, reflected in high levels of high-sensitivity C-reactive protein (hs-CRP), links excess adipose tissue to overproduction of pro-inflammatory cytokines.[7-9]

Adipose tissue, comprising adipocytes, pre-adipocytes, immune cells, and endothelial cells, responds to excessive nutrients through hypertrophy and hyperplasia. Severe obesity can induce hypoxia, triggering necrosis, macrophage infiltration, and increased inflammatory cytokine production.[10-12] In obese individuals, the activation of kinases such as c-Jun N-terminal kinase (JNK), inhibitor of kappa kinase (IKK), and protein kinase C (PKC) in adipose tissue and the liver regulates inflammatory cytokines.[13] These kinases also mediate transcription factors like activator protein-1 (AP-1) and interferon regulatory factor (IRF), amplifying inflammation and disrupting metabolic signaling.[14,15] Additionally, inflammasomes and Toll-like receptors (TLRs) in metabolic tissues propagate inflammatory responses. Inflammatory cytokines such as TNF-α and IL-6 stimulate liver cells to produce hs-CRP, linking obesity with systemic inflammation.[16]

2. Aim & Objectives

Recent studies have highlighted that low-grade inflammation in the pre-diabetic state is strongly associated with an increased risk of developing Type 2 diabetes and its complications. Chronic subclinical inflammation has also been established as a key component of insulin resistance syndrome.[15] This persistent low-grade inflammation impairs pancreatic beta-cell function, reducing insulin production and worsening insulin resistance, which collectively contribute to elevated blood glucose levels. This process not only accelerates the onset of diabetes but also predisposes individuals to complications, particularly cardiovascular diseases.[16] Epidemiological evidence largely supports these findings, although some studies have presented conflicting results.[17,18]

In response to these findings, we conducted a prospective, cross-sectional, descriptive, and observational hospital-based study targeting a reference population of pre-diabetic individuals across various age groups and sexes. The objective of the study was to identify high-risk individuals early on, allowing for timely lifestyle interventions and treatments to prevent the progression to Type 2 diabetes, cardiovascular diseases, and complications affecting the eyes, kidneys, and nervous system. Additionally, the study aimed to reduce the risk of cerebrovascular accidents (CVA).

3. Materials and Methods

This study was conducted at the outpatient clinics of the Department of Medicine, K.P.C. Medical College & Hospital, Jadavpur, Kolkata, over a period of one year from its inception. Patients were recruited from the outpatient Medicine Department of KPC Hospital. The study group consisted of 60 pre-diabetic patients aged 35 to 65 years, meeting criteria for Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), and HbA1c levels ranging from 5.7% to 6.4%, with or without a family history of diabetes. Additionally, a control group of 60 normoglycemic healthy individuals within the same age range was included. All biochemical analyses were conducted in the Department of Biochemistry at KPC Medical College & Hospital, Kolkata after taking ethical committee clearance.

3.1. Inclusion criteria

This study included Patients aged in between 35 to 65 years, Individuals diagnosed with IFG, IGT, or HbA1c between 5.7% and 6.4%, Patients with or without a family history of diabetes and healthy individuals aged 35 to 65 years were included as the control group.

3.2. Exclusion criteria

This study does not include Patients with a history of acute myocardial infarction, Patients with severe or chronic renal failure, Hyperglycemic crises (Fasting Blood Glucose ≥ 250 mg/dL, Postprandial Blood Glucose ≥ 300 mg/dL, or HbA1c > 10%), Severe hypertriglyceridemia (TG > 400 mg/dL) and Patients with acute injuries.

3.3. Selection criteria

1. Case Group: Individuals diagnosed with pre-diabetes, defined by Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), or HbA1c levels between 5.7% and 6.4%, aged 35 to 65 years, with or without a family history of diabetes.
2. Control Group: Healthy individuals of the same age group (35–65 years) without any history of pre-diabetes or diabetes.
3. Participants must not have any other serious medical conditions or be on medications that could interfere with the study outcomes.

The selection of patients was based on interviews, history-taking, and clinical examination. The clinical examinations included measurements of height, weight, skin tags, signs of pallor, edema, jaundice, cyanosis, clubbing, palpable neck glands, engorged neck veins, and the presence of Acanthosis Nigricans. Waist circumference, hip circumference, and neck circumference were also measured. Essential parameters, including pulse, blood pressure (BP), and temperature, were recorded. Overnight (12 hours) fasting venous blood samples were collected from both cases and controls for the estimation of fasting blood glucose, fasting insulin, lipid profile, TNF-Alpha, IL-6, and high-sensitivity C-reactive protein (hs-CRP). Fasting insulin, TNF-Alpha, and IL-6 levels were measured using their respective ELISA kits, while hs-CRP was estimated by latex-agglutination test in the Microbiology Department of KPC Medical College.

3.4. Sample size estimation

The sample size was calculated based on the expected prevalence of pre-diabetes in the target population and the power of the study. Sample size is calculated according to Fisher's formula of statistical analysis.The required sample size was determined to be 60 pre-diabetic individuals and 60 controls to achieve statistically significant results.

4. Result

A total of 60 pre-diabetic individuals were included in this study, consisting of 24 males and 36 females, aged between 35 and 65 years. An additional 60 healthy individuals, matched for age, were included as controls, comprising 32 males and 28 females. All biochemical parameters, including fasting blood glucose, fasting insulin, TNF-Alpha, IL-6, and hs-CRP, were significantly elevated in the pre-diabetic group compared to the healthy controls (**Table 1**,**Table 2**). HOMA-IR[19] was calculated using the formula: HOMA-IR = [Glucose x Insulin] / 22.5 (where glucose is in molar units, mmol/L)[20] or HOMA-IR = [Glucose x Insulin] / 405 (where glucose is in mass units, mg/dL),[21] and the results were statistically correlated with other findings using the Student's t-test.

Table 1: Levels of fasting blood sugar, fasting insulin & homa-ir of pre-diabetic individuals (cases) compared to that of control group.

Description	Fasting blood glucose (mg/dl)	Fasting insulin (micro iu/l)	homa-ir
Cases (N=60)	117.38	7.96	2.33
Controls (N=60)	83.32	5.51	1.19
T Value	13.85	8.07	6.12
Leveel of significance (p) value	0.00001	0.00001	0.00001

Table 2: Levels of TNF-Alfa, il-6 & hs-CRP of pre-diabetic individuals (cases) compared to that of control group.

Description	TNF-Alfa (pg/ml)	IL-6 (pg/ml)	hs-CRP(mg/dl)
Cases (n=60)	5.67	2.59	11.09
Controls (n=60)	3.65	0.97	5.11
T value	7.41	6.87	2.29
(p) value	0.00001	0.00001	0.00001

In this study, it was found that HOMA-IR is significantly (positively) correlated with two pro-inflammatory parameters, TNF-Alpha and IL-6, in the pre-diabetic study group. The correlation coefficient between HOMA-IR and TNF-Alpha was r = 0.925, which is highly significant with p = 0.00001 (**Figure 1**). IL-6 in pre-diabetics was also significantly and positively correlated with HOMA-IR, with a correlation coefficient of r = 0.766 at p = 0.00001 (**Figure 2**).

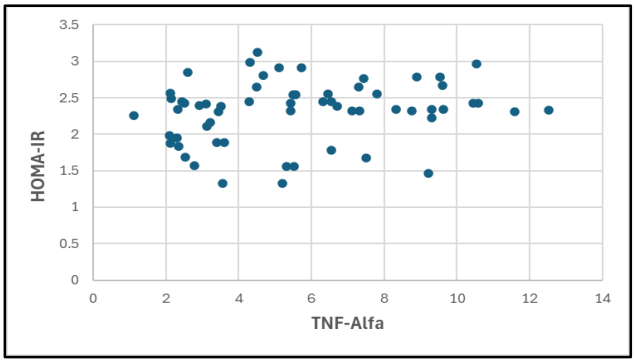

Figure 1: Scattered diagram showing correlation between TNF-ALFA & HOMA-IR

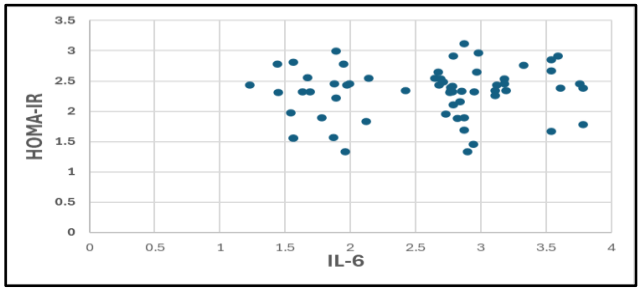

Figure 2: Scattered diagram showing correlation between IL-6 & HOMA-IR

In this study both TNF-Alfa & IL-6 are significantly correlated with hs-CRP of Pre-diabetic individuals (**Figure 3**, **Figure 4**).

Figure 3: Scattered diagram showing correlation between TNF-ALFA & hs-CRP

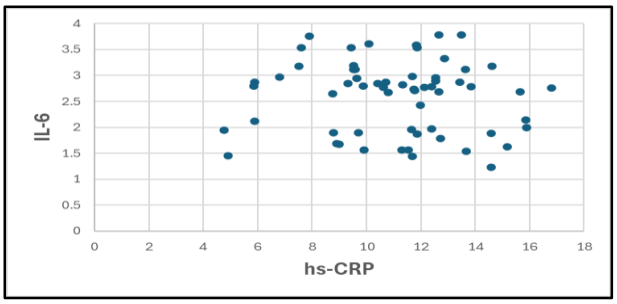

Figure 4: Scattered diagram showing correlation between IL-6 & hs-CRP

5. Discussion

This cross-sectional study evaluated inflammatory markers in sixty middle-aged individuals with central obesity, dyslipidemia, and pre-diabetes, defined by impaired fasting

glucose (IFG) and impaired glucose tolerance (IGT). The analysis showed significantly higher levels of fasting blood glucose, fasting insulin, TNF-α, IL-6, and hs-CRP in the pre-diabetic group compared to healthy controls, demonstrating an elevated inflammatory state. This supports existing research highlighting chronic low-grade inflammation as a central factor in the development of insulin resistance and related metabolic conditions (Hotamisligil et al., 1995);[23] (Fantuzzi, 2005).[6] Elevated TNF-α and IL-6 levels reflect the activation of immune pathways that disrupt normal insulin signaling, thus promoting insulin resistance, as reported by Vettor et al. (2005)[7] and Xu et al. (2003).[8] Furthermore, the strong positive correlations between HOMA-IR and both TNF-α (r = 0.925) and IL-6 (r = 0.766) in pre-diabetic individuals emphasize the connection between inflammation and insulin resistance. These findings align with Wallace et al. (2004),[19] who validated HOMA-IR as a reliable measure of insulin resistance and its association with inflammatory markers. Additionally, hs-CRP, a well-established marker of systemic inflammation, was also elevated in the pre-diabetic group and was positively correlated with both TNF-Alpha and IL-6. This further emphasizes the systemic nature of the inflammatory response in pre-diabetes. Bastard et al. (1999)[24] observed a similar association between IL-6 and hs-CRP in obese individuals, suggesting that these inflammatory markers are interrelated and contribute to the pathogenesis of metabolic diseases. This study identified significantly elevated hs-CRP levels in pre-diabetic individuals, indicating an enhanced inflammatory response that may function as a compensatory mechanism to counteract damage caused by insulin resistance. The positive correlation observed between hs-CRP and other inflammatory markers like TNF-α and IL-6 highlights the intricate relationship between adipose tissue, inflammation, and insulin resistance. Elevated hs-CRP levels in pre-diabetic individuals suggest an increased risk of cardiovascular diseases, as inflammation plays a key role in the development of atherosclerosis and related conditions. This finding is consistent with prior research by Pradhan et al. (2001),[26] which identified CRP as an independent predictor of Type 2 diabetes and cardiovascular risk. The observed rise in CRP and pro-inflammatory cytokines not only confirms systemic inflammation in pre-diabetic individuals but also points to potential future cardiovascular complications and cerebrovascular accidents (CVA) linked to insulin resistance. Research by Rajala & Scherer (2003)[15] and Hotamisligil (2006)[11] has shown that visceral fat is a significant source of pro-inflammatory cytokines like TNF-α and IL-6. This study supports these findings, with participants exhibiting higher levels of these cytokines, which are crucial in the onset of insulin resistance and metabolic dysfunction. These results are in agreement with earlier studies by Hermans et al. (1999)[9] and Bourlier & Bouloumie (2009),[10] which emphasize the pathological links between obesity, inflammation, and insulin resistance. The findings of this study reinforce the significant elevation of inflammatory markers in pre-diabetic individuals, highlighting the critical role of inflammation in the development of insulin resistance. The increased production of hs-CRP in response to internal damage serves as an early indicator, warning of potential cardiovascular and cerebrovascular complications in later stages of life. These results align with the hypothesis that chronic low-grade inflammation is a hallmark of the pre-diabetic state, emphasizing the need for early intervention to prevent progression to Type 2 diabetes and its related complications. Similar findings have been reported in several studies, which underscore the inflammatory pathways as key contributors to metabolic disorders and the increased risk of cardiovascular diseases (Pradhan et al., 2001);[26] (Hotamisligil, 2006);[11] (Vettor et al., 2005).[7]

6. Conclusion

Inflammation is a critical component of the immune system, initiating a protective response against harmful stimuli by mobilizing specific blood cells to target and eliminate harmful agents, as well as clear away damaged or dying cells.[23,24] In the case of pre-diabetes, the primary "threats" are believed to include elevated insulin levels resulting from an imbalance between blood glucose and insulin, a condition referred to as insulin resistance.[23] Individuals with obesity, especially those with central obesity (characterized by an increased waist circumference), frequently exhibit heightened low-grade systemic inflammation. This is largely driven by the expansion of visceral adipose tissue.[23,24] Dysfunction in adipose tissue impacts overall metabolism through various secretions that exert auto-, para-, and endocrine effects. Additionally, macrophage infiltration into visceral adipose tissue aggravates both chronic inflammation and hepatic insulin resistance.[24,25] Persistent low-grade inflammation, accompanied by elevated levels of inflammatory markers during pre-diabetes, significantly contributes to the development of Type 2 diabetes, insulin resistance, and beta-cell dysfunction, as evidenced by numerous studies.[25,26] The progression from metabolic irregularities, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to full-blown diabetes often spans several years. However, most individuals with pre-diabetes eventually develop diabetes, particularly those who are older, overweight, physically inactive, or possess additional risk factors.[26,27] This research underscores the necessity of early identification of high-risk pre-diabetic individuals. Early detection enables the introduction of lifestyle changes, dietary adjustments, weight management strategies, and appropriate therapeutic interventions to prevent the onset of Type 2 diabetes and mitigate associated complications, such as cardiovascular diseases and cerebrovascular accidents (CVA).

7. Source of Funding

None.

8. Conflict of Interest

None.

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