International Journal of Research in Medical Sciences
Lodha N. Int J Res Med Sci. 2026 Feb;14(2):506-511
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20260234

Original Research Article

Pathophysiological insights: insulin resistance and β-cell dysfunction as early markers of pre-diabetes

Niraj Lodha*

Department of Internal Medicine, Lodha Hospital and Research Centre, Pali, Rajasthan, India

Received: 09 October 2025
Revised: 13 November 2025
Accepted: 23 December 2025

***Correspondence:**
Dr. Niraj Lodha,
E-mail: nirajlodha2001@gmail.com

ABSTRACT

Background: Pre-diabetes represents a critical intermediate state of dysglycaemia where both insulin resistance (IR) and β-cell dysfunction (β-CD) contribute to progression toward type 2 diabetes mellitus (T2DM).
Methods: A cross-sectional study was conducted among 300 adults, divided into normal glucose tolerance (GT) (control n being 100), pre-T2DM (n being 120), and T2DM (n being 80) groups. Anthropometric and clinical measurements were documented, and biochemical assays were employed to calculate indices of IR (HOMA-IR, QUICKI, Matsuda index) and β-cell function (β-CF) (HOMA-β, insulinogenic index, disposition index, C-peptide). Logistic regression determined predictors of pre-T2DM, whereas ROC analysis evaluated discriminative efficacy.
Results: Participants with pre-T2DM and T2DM had greater BMI, waist circumference, and systolic blood pressure than NGT controls ($p<0.001$). IR measures exhibited a noteworthy stepwise worsening, characterized by increased HOMA-IR and decreased QUICKI and Matsuda indices ($p<0.001$). The function of β-cells deteriorated progressively among groups, evidenced by decreased HOMA-β, insulinogenic index, disposition index, and C-peptide levels ($p<0.001$). Logistic regression indicated that HOMA-IR ≥2.5 (OR being 3.48) and HOMA-β <100% (OR being 2.89) are noteworthy predictors of pre-T2DM. ROC analysis showed that the disposition index (AUC being 0.87) was the best way to tell the difference, better than measures of IR.
Conclusion: Both IR and β-CD are evident in pre-T2DM, but β-CD indices, particularly the disposition index, demonstrate superior predictive ability. These findings emphasize the need for early screening using combined indices beyond glucose levels to identify individuals at threat of progression.

Keywords: Pre-diabetes, IR, β-CD, HOMA-IR, Disposition index, Threat prediction

INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) is increasing, with approximately 470 million individuals affected by pre-T2DM worldwide; many of these individuals advance to clinical diabetes if early pathophysiological alterations are not identified and addressed. At the onset of this trajectory, two interconnected processes are believed to be pivotal: insulin resistance (IR) in peripheral tissues and the impaired function of pancreatic β-cells in their insulin secretion. It is essential to comprehend the manifestation of these changes prior to the diagnostic threshold of hyperglycemia for pre-T2DM prevention strategies.[1,2]

Recent research has clarified our understanding of β-CD, indicating that it is not merely a late occurrence, but rather one that initiates relatively early in the pre-T2DM phase. Research conducted over the past five years on human islet studies has demonstrated that abnormalities in insulin secretion machinery and gene regulatory networks manifest before noteworthy β-cell mass loss.[3] Likewise, individuals with normal GT were compared to those with pre-T2DM, revealing quantifiable β-cell deficits and insulin resistance, even among individuals still classified

as normoglycaemic by standard assessments.[4,5] The association between obesity, age, and central adiposity with insulin resistance (IR) is well established; however, their interaction with early β-cell dysfunction in specific populations has only recently been elucidated. The study elucidated the mechanisms by which pathways such as Hippo/YAP signaling, inflammation, oxidative stress, lipotoxicity, and endocrine stress compromise β-cell secretory function in prediabetes and early T2DM.[6] Studies have stressed that persistent β-CD (not just reduced mass) is an important early sign that could help tell the difference between people who are likely to move from pre-T2DM to T2DM.[5,6] In light of these developments, meticulous phenotypic characterization of both IR and β-CD in populations with NGT, pre-T2DM, and T2DM is essential to comprehend their relative timing, magnitude, and potential as early biomarkers. Detecting which indices of IR and β-CF best discriminate individuals at threat has important implications for screening, prevention and therapeutic targeting.[7] Hence the aim of the study is to elucidate the early pathophysiological changes in IR and β-CF across the spectrum of GT (normal, pre-T2DM, overt T2DM) in adults, in order to identify reliable early markers of pre-T2DM. To compare and quantify IR and β-CD markers among individuals with normal GT (NGT), pre-T2DM, and T2DM, and determine which indices have the greatest discriminatory performance (sensitivity, specificity, AUC) for identifying pre-T2DM.

METHODS

Study design and setting

This was a cross-sectional, analytical study conducted in the Department of Internal Medicine, Lodha Hospital and Research Centre, Pali, Rajasthan, India. The study was carried out during the defined study period (November 2024 to April 2025). A total of 300 adults were enrolled, and all procedures followed standard institutional protocols for participant recruitment, data collection, and laboratory analyses. Approval from the Institutional Ethics Committee was obtained prior to study initiation, and written informed consent was secured from all participants.

Experimental groups

Participants were allocated to three groups based on American Diabetes Association (ADA) criteria and OGTT results: control group as normal GT (NGT; n being 100), pre-T2DM (impaired fasting glucose and/or impaired GT; n being 120) and T2DM; n being 80. Adults aged 25–70 years presenting for metabolic screening, outpatient follow-up or referral were screened consecutively and enrolled until target group sizes were achieved.

Recruitment aimed to reflect routine clinical demographics with no deliberate matching; however, efforts were made to achieve balanced sex distribution across groups.

Inclusion criteria

Eligible participants were adults (25–70 years) able to complete an overnight fast and an OGTT.

Exclusion criteria

Key exclusion criteria were pregnancy or lactation; known type 1 diabetes or secondary diabetes; recent (within 4 weeks) acute illness or infection; chronic use of medications that alter glucose/insulin metabolism (systemic corticosteroids, chronic great-dose beta-agonists, atypical antipsychotics); active pancreatic disease; severe hepatic or renal impairment (eGFR<30 ml/min/1.73m² or transaminases >3×ULN); prior bariatric surgery; and inability or refusal to provide informed consent.

Data collection procedures

Each participant attended a single standardized study visit following a 10–12 hour overnight fast. A structured case report form captured demographic data, medical history, medication use and lifestyle factors. Anthropometry included body weight (kg), height (cm) and waist circumference (cm) measured using calibrated equipment and standard protocols; BMI was calculated as weight/height² (kg/m²). Blood pressure was recorded twice in the seated position after 5 minutes rest using an automated validated sphygmomanometer and averaged.

Laboratory methods and derived indices

Fasting blood samples were obtained for plasma glucose, insulin, C-peptide and HbA1c, a standard 75 g oral GT test (OGTT) was performed with blood draws at 0, 30 and 120 minutes for glucose and insulin to permit estimation of early-phase insulin secretion indices, laboratory assays for insulin and C-peptide used chemiluminescent immunoassays with documented quality control; glucose and HbA1c were measured using standardized enzymatic and HPLC methods respectively and derived indices included HOMA-IR and HOMA-β (from fasting glucose and insulin), QUICKI, Matsuda insulin sensitivity (IS) index (using OGTT values), the insulinogenic index (ΔInsulin 0–30/ΔGlucose 0–30) as a measure of early insulin response, and the disposition index (insulinogenic index×Matsuda index) as an integrated measure of β-cell compensation.

Clinical assessment and quality control

Trained study staff took measurements according to written standard operating procedures. Instruments were regularly calibrated, and laboratory assays included internal controls; technicians were blinded to the clinical group of participants whenever possible. Data were inputted into a secure database featuring double data entry and regular validation checks to reduce transcription errors.

Statistical analysis

Continuous variables are displayed as mean ± SD (or median [IQR] if non-normal); categorical variables are shown as counts and percentages. One-way ANOVA was used to compare groups for variables that were normally distributed, and Kruskal–Wallis tests were used for variables that were not. Chi-square tests were used for variables that were categorical. Multivariable logistic regression identified independent predictors of pre-T2DM (adjusted ORs with 95% CIs), utilizing covariates selected a priori (age, sex, BMI, waist circumference, HOMA-IR, HOMA-β). Model diagnostics encompassed goodness-of-fit evaluation and collinearity analysis. Receiver operating characteristic (ROC) analysis calculated the area under the curve (AUC) and the ideal cut points (Youden index) for potential markers, while DeLong's test was used to compare AUCs. A two-sided p-value of less than 0.05 indicated statistical significance. We used R version or statistical package for the social sciences (SPSS) version XX for the analyses, and all the steps could be repeated using the code that was written down.

RESULTS

The baseline characteristics of the study participants (n=300) exhibited some gradual disparities among the three groups. In patients with T2DM, the mean age was 51.39±10.3 years; 45.7±9.1 years in pre-T2DM; and 42.2±8.7 years in those with normal GT, and this difference was statistically significant (p<0.001). Gender distributions were almost identical in the groups, demonstrating no significant differences (p=0.82). The evaluations related to obesity and cardiovascular threats, however, kept shifting greatly.

The pre-T2DM and diabetes groups had a prominently greater BMI and waist circumference than the control group, indicating increased central obesity (p<0.001). Systolic blood pressure, however, greatly increased in all groups, with the diabetes group taking the greatest number (p<0.001). This indicates that age, obesity, and hypertension are catalytic operators advancing from normal GT to pre-T2DM and T2DM (Table 1).

Table 1: Baseline demographics and clinical characteristics of study participants (n=300).

Variables	Control (n=100)	Pre-diabetes (n=120)	T2DM (n=80)	P value
Age (years, mean±SD)	42.2±8.7	45.7±9.1	51.39±10.3	<0.001
Participants n (%)	54 (54%)	62 (51.7%)	44 (55%)	0.82
BMI (kg/m², mean±SD)	24.3±3.2	27.3±3.9	29.6±4.1	<0.001
Waist circumference (cm)	84.8±8.6	92.5±9.8	97.8±10.5	<0.001
Systolic BP (mmHg)	118.3±12.1	124.6±13.5	131.2±14.3	<0.001

The analysis of IR markers, as illustrated in Table 2 and Figure 1, demonstrated a distinct and significant progression from normal GT to pre-T2DM and T2DM. Fasting insulin levels greatly increased among groups, escalating from 6.77±2.5 µU/ml in controls to 11.31±3.9 µU/ml in pre-T2DM and 16.8±5.1 µU/ml in diabetes (p<0.001). Likewise, HOMA-IR readings exhibited a progressive increase, signifying deteriorating IR, whereas IS metrics, including QUICKI and the Matsuda index, shown substantial declines across groups (p<0.001). These findings demonstrate that the gradual decrease in insulin sensitivity and the consequent hyperinsulinemia are essential pathophysiological features associated with the transition from pre-T2DM to diabetes.

As shown in Figure 2 and Table 3 markers of β-CF revealed a progressive decline from normal GT to pre-T2DM and T2DM. HOMA-β levels were greatest in controls (141.3±28.5%) but dropped greatly in pre-T2DM (94.4±24.6%) and further in diabetes (58.78±20.3%) (p<0.001). Similarly, the insulinogenic index and disposition index, reflecting early insulin response and overall β-cell compensation, showed marked reductions across groups, with the lowest values in diabetes (p<0.001). C-peptide levels also decreased progressively, suggesting impaired endogenous insulin secretion. Overall, these results highlight that β-CD worsens greatly during the progression from pre-T2DM to diabetes, underscoring its critical role in disease pathogenesis.

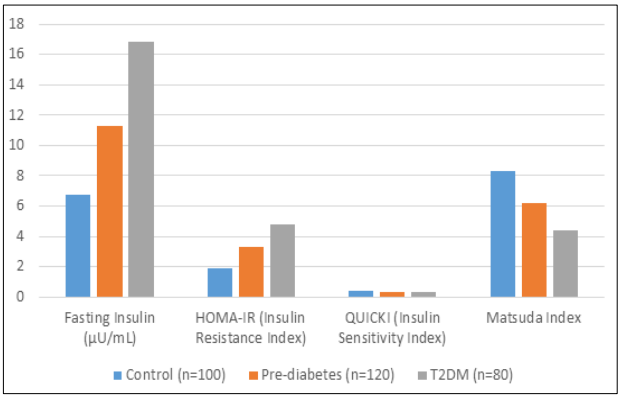

Figure 1: Comparison of IR markers across study groups.

The logistic regression analysis revealed multiple noteworthy predictors of pre-T2DM. People who were older than 45 had a moderately greater threat (OR being 1.82, 95% CI: 1.12–2.96, p being 0.015). If and when obesity-related parameters are considered, with weight and stature of BMI ≥27 kg/m² bearing ORs at 2.56, p<0.001, and waist circumference >90 cm bearing ORs at 2.12, p=0.002, then they exhibit significant correlation with pre-

T2DM. Conversely, metabolic markers show the best predictability, with HOMA-IR ≥2.5 almost tripling the risk at an OR of 3.48, p<0.001, and HOMA-β <100% almost tripling it at an OR of 2.89, p<0.001. Thus, from a clinical risk indicator standpoint, these two factors of obesity and early disturbances in IR and β-CF become the prominent ones in determining pre-T2DM threat (Table 4). The ROC curve has shown that both methods of measuring IR and β-CD measurements are good at predicting pre-T2DM. HOMA-IR did excellent in distinguishing (with the AUC value being 0.82) and considering an equal balance of sensitivity (78%) and specificity (74%). QUICKI fared a little worse (its AUC was 0.79). β-CF markers, however, worked better as a group. The HOMA-β (AUC=0.85) and the insulinogenic index (AUC=0.83) were both very good at predicting what would happen. The disposition index, however, was the best at telling the groups apart (AUC=0.87), with a sensitivity of 82% and a specificity of 81%. These findings indicate that β-CD markers, particularly the disposition index, may be more efficacious than IR markers in identifying individuals predisposed to pre-T2DM (Table 5).

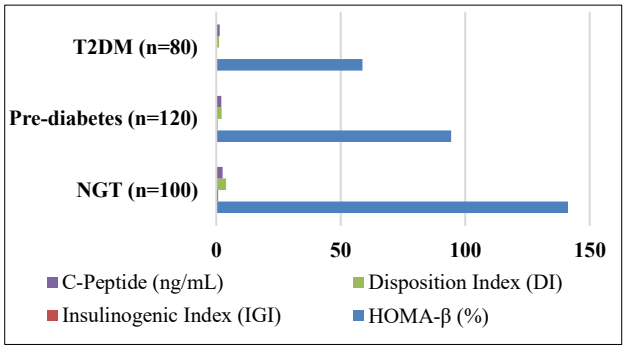

Figure 2: Comparison of β-CD markers across study groups.

Table 2: Insulin resistance markers across groups.

Marker (IR)	Control (n=100)	Pre-diabetes (n=120)	T2DM (n=80)	P value
Fasting insulin (µU/ml)	6.77±2.5	11.31±3.9	16.8±5.1	<0.001
HOMA-IR (insulin resistance index)	1.88±0.7	3.33±1.1	4.79±1.6	<0.001
QUICKI (insulin sensitivity index)	0.37±0.04	0.33±0.03	0.30±0.03	<0.001
Matsuda index	8.3±2.1	6.23±1.8	4.4±1.5	<0.001

Table 3: β-cell dysfunction markers across groups.

Marker (β-CD)	Control (NGT n=100)	Pre-diabetes (n=120)	T2DM (n=80)	P value
HOMA-β (%)	141.3±28.5	94.4±24.6	58.78±20.3	<0.001
Insulinogenic index (IGI)	0.75±0.22	0.46±0.18	0.26±0.15	<0.001
Disposition index (DI)	3.9±1.2	2.1±0.9	1.1±0.6	<0.001
C-Peptide (ng/ml)	2.6±0.8	2.0±0.7	1.4±0.6	<0.001

Table 4: Logistic regression analysis of risk factors for pre-diabetes.

Predictor variable	Odds ratio (OR)	95% CI	P value
Age >45 years	1.82	1.12–2.96	0.015
BMI ≥27 kg/m²	2.56	1.54–4.25	<0.001
Waist circumference >90 cm	2.12	1.30–3.45	0.002
HOMA-IR ≥2.5	3.48	2.05–5.91	<0.001
HOMA-β <100%	2.89	1.72–4.86	<0.001

Table 5: ROC curve analysis of IR and β-cell dysfunction markers for predicting pre-diabetes.

Marker	AUC	95% CI	Sensitivity (%)	Specificity (%)
HOMA-IR	0.82	0.77–0.87	78	74
QUICKI	0.79	0.73–0.85	72	76
HOMA-β	0.85	0.80–0.90	80	78
Insulinogenic index	0.83	0.77–0.88	76	79
Disposition index	0.87	0.82–0.91	82	81

DISCUSSION

This study investigated the combined effects of IR and β-CD throughout the continuum of normal GT, pre-T2DM, and T2DM. Our results show that metabolic and biochemical markers get worse in steps, which shows how they work together in the early stages of dysglycaemia.

Baseline data indicated that participants with pre-T2DM and T2DM were older and exhibited elevated BMI, waist circumference, and blood pressure relative to controls, aligning with evidence that associates central obesity and age with compromised glucose regulation.[6,8] These traits reflect the well-established influence of adiposity and cardiometabolic stress on IS.

IR markers revealed progressive hyperinsulinaemia and worsening HOMA-IR, with declines in QUICKI and Matsuda index. This aligns with recent reports indicating that compensatory hyperinsulinaemia characterises pre-T2DM but becomes inadequate as T2DM develops.[9,10]

β-CD markers also declined greatly, with reductions in HOMA-β, insulinogenic index, disposition index, and C-peptide. This supports emerging evidence that β-cell impairment begins before overt diabetes and is decisive in disease progression.[11] The reduced disposition index highlights inadequate β-cell compensation in the face of rising IR. Regression analysis identified both adiposity and metabolic indices (HOMA-IR ≥2.5, HOMA-β <100%) as strong predictors of pre-T2DM, consistent with recent longitudinal findings.[12]

ROC analysis demonstrated that β-cell indices, particularly the disposition index, provided the greatest discriminative power, echoing newer evidence that integrated measures outperform single indices for threat prediction.[13-15]

Although limited by its cross-sectional design, single-centre setting, and reliance on surrogate indices rather than gold-standard techniques, this study reinforces that both IR and β-CD contribute to pre-T2DM, with β-cell failure ultimately driving progression. These findings underscore the need for early screening using combined indices of IS and secretion. In summary, this study underscores the dual contribution of IR and β-CD in the progression from normal GT to pre-T2DM and T2DM. While both mechanisms deteriorate in parallel, impaired β-cell compensation appears to be the decisive factor driving disease onset.

The superior predictive accuracy of the disposition index highlights its potential as a valuable early marker for identifying great-threat individuals. These findings reinforce the need for early, multidimensional screening strategies that extend beyond glucose levels alone, integrating surrogate indices of IS and β-CF to improve prevention and timely intervention.

CONCLUSION

This study demonstrates that both IR and β-CD progressively worsen across the spectrum from normal GT to diabetes, with β-CD emerging as the stronger predictor of pre-T2DM. The disposition index showed the greatest discriminative accuracy, underscoring its value as a potential early marker for targeted interventions.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Lodha N. Pathophysiological insights: insulin resistance and β-Cell dysfunction as early markers of pre-diabetes. Int J Res Med Sci 2026;14:506-11.