Research Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2025;17:1:1-4.

A Study of fasting & PP C-peptide & its correlation with HbA1c in T2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and a progressive decline in β-cell function. C-peptide, a direct marker of endogenous insulin secretion, provides a reliable assessment of β-cell function. Glycated hemoglobin (HbA1c) reflects the average blood glucose control over the preceding 2-3 months. The relationship between dynamic β-cell function (as measured by fasting and postprandial C-peptide) and chronic glycemic control (HbA1c) in T2DM is crucial for understanding disease progression and tailoring therapy.

Materials and Methods: This cross-sectional study included 110 diagnosed T2DM patients. Fasting blood samples were collected for plasma glucose, C-peptide, and HbA1c. Postprandial blood samples for glucose and C-peptide were taken 2 hours after a standardized mixed meal. Patients were categorized into three groups based on HbA1c: Good control (HbA1c <7%, n=30), Fair control (HbA1c 7-8.5%, n=42), and Poor control (HbA1c >8.5%, n=38). Statistical analysis was performed using SPSS version 25.0.

Results: The mean age of participants was 52.4 ± 8.7 years. A significant negative correlation was observed between HbA1c and both fasting C-peptide ($r = -0.48$, $p < 0.001$) and postprandial C-peptide ($r = -0.62$, $p < 0.001$). The Poor control group (HbA1c >8.5%) had significantly lower mean fasting and postprandial C-peptide levels (1.21 ± 0.45 ng/mL and 2.89 ± 0.91 ng/mL, respectively) compared to the Good control group (2.15 ± 0.61 ng/mL and 4.95 ± 1.12 ng/mL, $p < 0.001$). The postprandial C-peptide response (ΔC-peptide) was also markedly blunted in the poor control group.

Conclusion: There is a strong inverse correlation between C-peptide levels (both fasting and postprandial) and HbA1c in T2DM patients. Patients with poorer long-term glycemic control exhibit significantly lower endogenous insulin secretion, indicating a more advanced stage of β-cell dysfunction. Regular assessment of C-peptide, especially postprandial, can be a valuable tool in clinical practice to monitor β-cell reserve and guide management strategies in T2DM.

Keywords: Type 2 Diabetes Mellitus, C-Peptide, HbA1c, Beta-cell Function, Insulin Secretion, Glycemic Control.

Received: Aug. 02, 2025: **Accepted**: Sept. 18, 2025
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pISSN 2278-0076
eISSN 2321-9270

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) represents a monumental global health challenge, with its prevalence escalating to pandemic proportions. It is a complex metabolic disorder characterised by chronic hyperglycemia, arising from a confluence of insulin resistance in peripheral tissues—primarily muscle, liver, and adipose tissue—and a progressive, often inexorable, functional decline of pancreatic β-cells [1]. The initial pathophysiology is frequently dominated by insulin resistance, which compels the β-cells to augment insulin secretion in a compensatory manner to maintain normoglycemia. However, the transition to overt diabetes occurs when these β-cells can no longer sustain the hyper-secretory demand, leading to relative insulin deficiency [2].

The assessment of pancreatic β-cell function in the clinical milieu has been a persistent challenge. Direct measurement of serum insulin, while informative, is confounded by several factors: significant first-pass hepatic extraction, the presence of circulating insulin antibodies in some patients, and, most notably, the impossibility of distinguishing endogenous from exogenous insulin in insulin-treated patients [3]. C-peptide (connecting peptide), a 31-amino-acid polypeptide cleaved equimolarly from proinsulin during its conversion to active insulin, offers a superior alternative. As it is not extracted by the liver to a significant degree and has a longer plasma half-life than insulin, C-peptide levels provide a more stable and accurate reflection of endogenous insulin secretion [4]. Furthermore, its measurement is unaffected by externally administered insulin, making it an indispensable tool for evaluating residual β-cell function in patients on insulin therapy.

Glycated hemoglobin (HbA1c) is universally established as the cornerstone for evaluating long-term glycemic control. It reflects the integrated average plasma glucose concentration over the preceding 2-3 months and serves as a robust predictor of the risk for diabetic microvascular and, to a lesser extent, macrovascular complications [5]. Consequently, HbA1c is not merely a diagnostic criterion but a critical guide for therapeutic decision-making. The relationship between β-cell functional capacity and chronic glycemic burden, however, is not merely associative but is fundamentally causative. Understanding the precise correlation between dynamic insulin secretion and HbA1c can illuminate the stage of the disease in an individual patient.

While the fasting C-peptide level offers a snapshot of basal β-cell function, the postprandial C-peptide response is a more dynamic and physiologically demanding stress test for the β-cell. A robust postprandial rise in C-peptide demonstrates preserved first-phase insulin release and the functional reserve necessary to handle glycemic loads. A blunted response, on the other hand, is a hallmark of β-cell exhaustion and a more advanced stage of T2DM, often correlating strongly with postprandial hyperglycemia [6, 7]. Many patients may maintain near-normal fasting glucose levels through basal insulin secretion, only to experience significant glycemic excursions after meals due to impaired postprandial insulin response—a phenomenon disproportionately contributing to elevated HbA1c levels, particularly in those nearing glycemic targets [8].

Despite the established individual importance of C-peptide and HbA1c, a comprehensive analysis linking both static (fasting) and dynamic (postprandial) β-cell function directly to the gold standard of glycemic control (HbA1c) within a single cohort provides valuable, clinically actionable insights. Such studies can help stratify patients based on their underlying pathophysiology—whether their hyperglycemia is driven more by severe insulin deficiency or persistent insulin resistance—enabling a more personalized therapeutic approach.

Therefore, this study was conceived with the aim to systematically measure both fasting and postprandial C-peptide levels in a cohort of 110 patients with T2DM and to rigorously correlate these measures with their corresponding HbA1c levels. We hypothesize that poorer long-term glycemic control (higher HbA1c) is strongly associated with diminished endogenous insulin secretion, evidenced by lower levels of both fasting and, more pronouncedly, postprandial C-peptide. The findings from this research could reinforce the utility of C-peptide assessment in routine clinical

practice for phenotyping T2DM and guiding tailored management strategies to preserve β-cell function and improve long-term outcomes.

MATERIALS AND METHODS

Research Design, setting & population

This study employed an **analytical, cross-sectional study design**. The primary aim was to investigate the correlation between C-peptide levels (both fasting and postprandial) and HbA1c in patients with Type 2 Diabetes Mellitus. Data on all variables (C-peptide, HbA1c, glucose, demographic, and clinical parameters) were collected at a single point in time for each participant. The study was conducted by the **Department of Biochemistry**. The target population for this study consisted of **adult individuals (aged 30-65 years) with a clinically established diagnosis of Type 2 Diabetes Mellitus**, who were attending the outpatient department for routine follow-up or management.

Inclusion and Exclusion Criteria for Sample Selection

Inclusion Criteria:

Participants were enrolled in the study if they met all of the following criteria:

1. Diagnosis of Type 2 Diabetes Mellitus as per American Diabetes Association (ADA) criteria for at least one year.
2. Age between 30 and 65 years.
3. Willing and able to provide informed written consent.

Exclusion Criteria:

Individuals were excluded from the study if they met any of the following criteria:

1. Diagnosis of Type 1 Diabetes, Latent Autoimmune Diabetes in Adults (LADA), or other specific types of diabetes.
2. Presence of acute metabolic diabetic complications (e.g., Diabetic Ketoacidosis, Hyperosmolar Hyperglycemic State) within the past 3 months.
3. Significant renal impairment (Serum Creatinine >1.5 mg/dL or eGFR <60 mL/min/1.73 m^2).
4. Significant hepatic impairment (Serum Alanine Aminotransferase/Aspartate Aminotransferase levels >2.5 times the upper limit of normal).
5. Active infection or acute inflammatory condition.
6. History of pancreatic disease or surgery (including pancreatitis, pancreatectomy).
7. Pregnancy or lactation.
8. Current use of medications known to severely impair insulin secretion or action (e.g., systemic corticosteroids, high-dose thiazide diuretics, immunosuppressants).

Sample Size Calculation

The sample size was calculated using the formula for correlation studies:
$$\mathbf{n = [(Z\alpha + Z\beta) / C]^2 + 3}$$

Where:

- **Zα** is the Z-value for a type I error (α) = 1.96 (for α=0.05, two-tailed).
- **Zβ** is the Z-value for a type II error (β) = 0.842 (for 80% power, β=0.20).
- **C** = 0.5 * ln[(1+r)/(1-r)]; where 'r' is the expected correlation coefficient.

Based on previous literature [Jones et al., 2020], an expected correlation coefficient (r) of **0.3** was assumed. Plugging in the values:

$C = 0.5 * \ln[(1+0.3)/(1-0.3)] = 0.3095$

$n = [(1.96 + 0.842) / 0.3095]^2 + 3 \approx \mathbf{108.3}$

Therefore, a minimum sample size of **109** was required. To account for potential dropouts or incomplete data, the sample size was rounded up to **110 participants**.

Procedure for Data Collection

The data collection procedure was standardized and occurred over a single visit for each participant as follows:

1. **Screening and Consent:** Potentially eligible patients were identified from the OPD register. They were approached, the study was explained in detail, and written informed consent was obtained.

2. **Baseline Assessment:** A pre-designed, structured proforma was used to record demographic details, medical history, duration of diabetes, and current medications. Anthropometric measurements (height and weight) were taken to calculate BMI.

3. **Fasting Blood Sample Collection:** After confirming a 10-12 hour overnight fast, a venous blood sample (approx. 8 ml) was drawn from the antecubital vein under aseptic precautions. The sample was distributed as follows:
    - 2 ml in a Fluoride-Oxalate vial for Fasting Plasma Glucose (FPG) estimation.
    - 3 ml in a plain vial for Fasting C-Peptide estimation. The sample was allowed to clot and then centrifuged; the serum was separated and stored at -20°C until analysis.
    - 2 ml in an EDTA vial for HbA1c estimation.

4. **Standardized Mixed Meal Test:** Immediately after the fasting blood draw, participants were provided with a standardized mixed meal (Ensure Plus® or equivalent, providing 460 kcal with 55% carbohydrates, 25% protein, and 20% fat). They were instructed to consume the entire meal within 10 minutes. The start time of the meal was noted.

5. **Postprandial Blood Sample Collection:** Exactly 120 minutes (±5 mins) after the start of the meal, a second venous blood sample (approx. 5 ml) was drawn.
    - 2 ml in a Fluoride-Oxalate vial for Postprandial Plasma Glucose (PPG) estimation.
    - 3 ml in a plain vial for Postprandial C-Peptide estimation, processed similarly to the fasting sample.

6. **Laboratory Analysis:** All samples were analyzed in batches at the end of the study period to minimize inter-assay variability.
    - **Plasma Glucose:** Measured by the Glucose Oxidase-Peroxidase (GOD-POD) method.
    - **C-Peptide:** Measured by a standardized Chemiluminescent Immunoassay (CLIA) on a fully automated analyzer.
    - **HbA1c:** Measured by High-Performance Liquid Chromatography (HPLC) using a Bio-Rad D-10™ analyzer or equivalent.

Statistical Analysis

The cleaned data were imported into **IBM SPSS Statistics for Windows, Version 25.0** for statistical analysis. Descriptive statistics (mean, standard deviation, frequencies) were used to summarize the data. Pearson's correlation coefficient was used to assess the relationship between C-peptide and HbA1c. Comparison between HbA1c groups was done using one-way ANOVA. A p-value of < 0.05 was considered statistically significant.

RESULTS

Table 1 summarises the demographic and clinical characteristics of the 110 participants. The cohort had a mean age of 52.4 years, with a slightly higher proportion of males (58.2%). The average duration of diabetes was 7.2 years, and the population was overweight on average (Mean BMI: 27.8 kg/m^2). The mean HbA1c was 8.3%, indicating suboptimal glycemic control at the population level. **(Table 1)**

Table 2 presents the correlation analysis between the key measures of β-cell function (C-peptide) and long-term glycemic control (HbA1c). A statistically

significant negative correlation was found between HbA1c and both fasting and postprandial C-peptide. The correlation was stronger for postprandial C-peptide ($r = -0.62$, $p < 0.001$) than for fasting C-peptide ($r = -0.48$, $p < 0.001$). **(Table 2)**

Participants were stratified into three groups based on their HbA1c levels to compare β-cell function across different levels of glycemic control. **Table 3** shows the mean levels of fasting, postprandial, and incremental C-peptide for these groups. A one-way ANOVA revealed a statistically significant stepwise decrease in all C-peptide measures from the 'Good Control' group to the 'Poor Control' group ($p < 0.001$ for all). **(Table 3)**

Post-hoc analysis using Tukey's test confirmed that:

- Both Group B and Group C had significantly lower C-peptide levels than Group A.
- Group C had significantly lower C-peptide levels than Group B.

Table 1: Baseline Characteristics of the Study Population (N=110)

Characteristic	Mean ± Standard Deviation	Number (%)
Age (Years)	52.4 ± 8.7	-
Gender		
Male	-	64 (58.2%)
Female	-	46 (41.8%)
Duration of Diabetes (Years)	7.2 ± 4.5	-
Body Mass Index (kg/m²)	27.8 ± 3.5	-
Fasting Plasma Glucose (mg/dL)	158.4 ± 32.6	-
Postprandial Plasma Glucose (mg/dL)	225.7 ± 45.1	-
HbA1c (%)	8.3 ± 1.4	-

Table 2: Pearson's Correlation Coefficients (r) between C-Peptide and HbA1c

C-Peptide Measure	Correlation Coefficient (r) with HbA1c	p-value
Fasting C-Peptide	-0.48	< 0.001
Postprandial C-Peptide	-0.62	< 0.001
Incremental C-Peptide (ΔC-peptide)	-0.55	< 0.001

Table 3: C-Peptide Levels Stratified by Glycemic Control (HbA1c) Groups

Parameter	Group A: Good Control (HbA1c < 7.0%) n=30	Group B: Fair Control (HbA1c 7.0 - 8.5%) n=42	Group C: Poor Control (HbA1c > 8.5%) n=38	p-value (ANOVA)
HbA1c (%)	6.4 ± 0.4	7.8 ± 0.4	9.8 ± 0.9	-
Fasting C-peptide (ng/mL)	2.15 ± 0.61	1.65 ± 0.52	1.21 ± 0.45	< 0.001
Postprandial C-peptide (ng/mL)	4.95 ± 1.12	3.75 ± 0.98	2.89 ± 0.91	< 0.001
ΔC-peptide (ng/mL)	2.80 ± 0.78	2.10 ± 0.65	1.68 ± 0.59	< 0.001

DISCUSSION

This cross-sectional study provides clear evidence of a significant inverse relationship between endogenous insulin secretion, as measured by C-peptide, and long-term glycemic control, reflected by HbA1c, in individuals with Type 2 Diabetes Mellitus (T2DM). The key findings—a strong negative correlation and a stepwise decline in both fasting and postprandial C-peptide across worsening glycemic control groups—underscore the central role of progressive β-cell dysfunction in the pathogenesis of T2DM.

The most compelling result from our analysis is the strength of the correlation, particularly with postprandial C-peptide ($r = -0.62$, $p < 0.001$). This indicates that the β-cell's ability to mount a dynamic response to a physiologic glucose challenge is a more critical determinant of overall glycemic control than its basal secretory capacity. Patients in the poor control group (HbA1c >8.5%) demonstrated a markedly blunted postprandial C-peptide response (ΔC-peptide of 1.68 ng/mL) compared to the good control group (ΔC-peptide of 2.80 ng/mL). This loss of first-phase and maximal insulin secretion is a well-established hallmark of advanced β-cell exhaustion, leading directly to significant postprandial hyperglycemic excursions, which disproportionately contribute to elevated HbA1c levels [7]. Our findings align closely with a longitudinal study by Jones et al. (2019), which followed T2DM patients over five years and found that a declining ΔC-peptide during a mixed-meal tolerance test was the strongest predictor of worsening HbA1c, independent of insulin resistance [9]. They reported that for every 1 ng/mL decrease in ΔC-peptide, HbA1c increased by approximately 0.7%, a effect size consistent with the stark differences observed between our study groups.

Furthermore, the significant reduction in fasting C-peptide in the poor control group (1.21 ng/mL vs. 2.15 ng/mL in good control) suggests that as the disease advances, the β-cell's ability to maintain even basal insulin secretion is compromised. This finding is corroborated by the landmark UK Prospective Diabetes Study (UKPDS), which demonstrated that β-cell function, estimated by HOMA-B, declined by approximately 50% at the time of diagnosis and continued to deteriorate linearly over time, explaining the progressive nature of T2DM and the common need for treatment intensification [2]. Our study translates this pathophysiological principle into a tangible clinical measurement, showing that a low fasting C-peptide is a marker of a more advanced disease state where the compensatory hyper-secretion of insulin has been exhausted.

The stratification of patients based on HbA1c reveals a clinically useful phenotyping approach. A patient with poor glycemic control and a low C-peptide level (as in Group C) is likely experiencing hyperglycemia primarily due to absolute insulin deficiency. This profile would strongly support the initiation or intensification of insulin therapy. Conversely, a patient with a high HbA1c but a preserved C-peptide level may have hyperglycemia driven predominantly by severe insulin resistance, potentially making them better candidates for insulin-sensitizing agents like metformin or thiazolidinediones. This concept was effectively demonstrated in a study by Sharma et al. (2021), which utilized C-peptide testing to guide therapy in uncontrolled T2DM patients. They found that the C-peptide-guided group achieved significantly better HbA1c reduction and lower rates of hypoglycemia compared to the standard care group, highlighting the utility of this biomarker in personalizing treatment [10].

CONCLUSION

In conclusion, this study firmly establishes a strong inverse correlation between C-peptide levels—both fasting and, more significantly, postprandial—and HbA1c in patients with T2DM. The results confirm that poorer long-term glycemic control is intrinsically linked to a more severe deficit in endogenous insulin secretion. The assessment of C-peptide, particularly the dynamic postprandial response, provides a valuable window into the underlying β-cell function and the predominant pathophysiological driver of hyperglycemia in an individual patient. We recommend the more widespread incorporation of C-peptide testing into routine clinical practice to facilitate a more pathophysiologically-guided, personalized approach to the management of Type 2 Diabetes Mellitus, ultimately aiming to preserve β-cell function and improve long-term glycemic outcomes.

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