SERUM C-PEPTIDE LEVELS IN NEWLY DIAGNOSED ADULT DIABETES PATIENTS: A CROSS-SECTIONAL STUDY FROM SOUTH INDIA

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Abstract. Background: *Accurate assessment of pancreatic beta-cell function in diabetes diagnosis is important for prognosis and individualized management. C-peptide is a reliable biomarker of endogenous insulin secretion, but data from treatment-naïve South Asian adults are limited.* ***Materials and Methods:*** *Single-center cross-sectional study in Salem, South India, including 100 adults (18-70 years) with newly diagnosed diabetes (< 6 months) and minimal treatment exposure. Fasting and glucagon-stimulated serum C-peptide were measured, with clinical and metabolic profiling and targeted autoantibody testing when indicated.* ***Results:*** *Mean fasting C-peptide was 1.62 ± 0.72 ng/mL and stimulated C-peptide was 2.53 ± 1.01 ng/mL. Low β-cell reserve (< 0.8 ng/mL fasting and/or < 1.8 ng/mL stimulated) was present in 29%. C-peptide showed no clinically meaningful correlation with HbA1c, fasting glucose, BMI, or HOMA indices. Subtype classification suggested 65% T2D-like, 21% possible autoimmune (LADA), and 14% indeterminate.* ***Conclusions:*** *Adults with newly diagnosed diabetes in South India show substantial heterogeneity in β-cell reserve, with nearly one-third having low C-peptide at presentation. Integrating C-peptide (and selective autoantibody testing) may improve early clinical stratification.*

Key words: *serum C-peptide, newly diagnosed diabetes, beta-cell function, autoantibodies, South Asian population, diabetes heterogeneity, autoimmune diabetes, LADA, beta-cell reserve, glucagon stimulation test*

Introduction

Diabetes mellitus is a major global health challenge, with more than 400 million affected adults and projections are expected to exceed 600 million in the coming decades [1, 2]. South Asia, particularly India, carries a disproportionately high burden, characterized by earlier age of onset, high prevalence even at normal BMI, and rapid progression to complications [3, 4]. These features suggest important ethnic and pathophysiological differences compared with Western populations.

Type 2 diabetes mellitus (T2DM) is classically attributed to a combination of insulin resistance and progressive pancreatic β-cell failure [5]. However, mounting evidence indicates substantial heterogeneity: some individuals develop diabetes predominantly due to severe insulin resistance with preserved β-cell reserve, whereas others show marked β-cell deficiency despite modest insulin resistance [6]. In addition, a sizeable subset of adults initially labelled as having T2DM actually have latent autoimmune diabetes in adults (LADA) or other non-classical forms of diabetes [7]. This heterogeneity has major implications for prognosis and treatment selection, yet is rarely assessed systematically in routine practice.

C-peptide, secreted in equimolar amounts with endogenous insulin, is a robust biomarker of β-cell secretory capacity because it is not subject to significant hepatic first-pass extraction and has more stable kinetics than insulin [8]. Measurement of fasting and stimulated C-peptide can quantify β-cell reserve and help distinguish classical T2DM from LADA and other atypical subtypes [9]. Despite this, standardized C-peptide assessment is not routinely incorporated into diagnostic work-up for newly diagnosed adult diabetes, particularly in low- and middle-income settings.

Data on C-peptide distribution in newly diagnosed, treatment-naïve adults from South Asia are limited, and most existing studies originate from Western populations with different ethnic, genetic, and environmental backgrounds [10]. Whether C-peptide provides information beyond conventional markers, such as HbA1c, fasting glucose, BMI, and HOMA indices at the time of diagnosis, remains unclear in this high-risk region.

Therefore, the present study aimed to characterize fasting and glucagon-stimulated serum C-peptide levels in newly diagnosed adult diabetes patients in South India, estimate the proportion with low β-cell reserve, examine relationships between C-peptide and standard metabolic markers, and explore a pragmatic subtype classification framework integrating C-peptide, autoantibodies, and clinical phenotype.

Materials and methods

Study design and setting

This study was planned as a single-centre, observational, cross-sectional examination. It was carried out in the Department of General Medicine at Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals (VMKVMCH), a 500-bed tertiary care teaching institution in Salem, Tamil Nadu, India. The hospital functions as a referral centre for diabetes and endocrine disorders. Patient enrolment and data collection were performed over a 12-month period from 1 January to 31 December 2024.

Study population

Adults between 18 and 70 years of age with a recent diagnosis of diabetes mellitus were considered for inclusion. “Newly diagnosed” was defined as a diagnosis made within the preceding six months. Diabetes was diagnosed according to standard criteria: elevated fasting plasma glucose, abnormal 2-hour plasma glucose on a 75-g oral glucose tolerance test, raised HbA1c, or random plasma glucose ≥ 200 mg/dL in the presence of classical symptoms such as polyuria, polydipsia or weight loss. Only patients who were either treatment-naïve or had received oral antidiabetic drugs for ≤ 14 days and had no prior exposure to insulin were enrolled.

Patients were excluded if they had a known history of type 1 diabetes or previous diabetic ketoacidosis, evidence of pancreatic disease (acute or chronic pancreatitis, prior pancreatectomy, cystic fibrosis–related diabetes or haemochromatosis), an estimated glomerular filtration rate below 60 mL/min/1.73 m², pregnancy or lactation, recent systemic glucocorticoid use within the last four weeks, acute severe intercurrent illness, prior solid organ transplantation, documented allergy or contraindication to glucagon, or if they were unable or unwilling to provide written informed consent.

Recruitment and informed consent

Potential participants were identified from the General Medicine and Endocrinology outpatient clinics, from referrals by primary health centres, and among patients attending the emergency department with hyperglycaemia or related complaints. The study objectives, procedures, possible risks and anticipated benefits were explained in detail in the participant’s preferred language (Tamil, Telugu or English). Written informed consent was obtained from all participants before any study-specific procedure was undertaken.

Clinical assessment and anthropometry

All evaluations were conducted at a single morning visit scheduled between 08:00 and 10:00 o’clock, after an overnight fast of 8-10 hours. A structured proforma was used to record demographic details, mode of presentation, time since diagnosis, family history of diabetes and autoimmune disease, coexisting illnesses, and current or past medication use. Lifestyle information, including tobacco use, alcohol intake, physical activity and broad dietary patterns, was also collected.

Body weight and height were measured using calibrated equipment, with participants wearing light clothing and no footwear. Body mass index (BMI) was calculated as weight (kg)/height² (m²). Waist circumference was measured at the midpoint between the lower costal margin and iliac crest using a non-stretchable tape. Blood pressure was recorded in the seated position after at least five minutes of rest; two readings were taken two minutes apart and the mean value was used. A focused physical examination was performed with emphasis on cardiovascular, abdominal and basic neurological findings.

Laboratory procedures

Fasting venous blood samples were collected into appropriate vacutainer tubes for biochemical and hormonal estimation. After centrifugation, serum and plasma were separated and stored at − 20° C until batch analysis. Fasting plasma glucose, lipid profile, liver enzymes and serum creatinine were measured using standard automated methods. HbA1c was determined by high-performance liquid chromatography. Where indicated, thyroid-stimulating hormone was also measured.

Serum C-peptide was quantified on an automated platform using a two-step chemiluminescent immunoassay in an accredited laboratory, following the manufacturer’s instructions.

Glucagon stimulation test

Immediately after fasting blood sampling, stimulated C-peptide was assessed using an intravenous glucagon stimulation test: 1 mg glucagon was administered intravenously over 30-60 seconds, and a stimulated C-peptide sample was collected at 6 minutes (acceptable window 4-8 minutes).

Autoantibody testing

Participants with reduced C-peptide values or clinical features suggesting autoimmune diabetes (younger age at onset, lean body habitus or abrupt presentation) underwent testing for glutamic acid decarboxylase (GAD65) and islet cell antibodies and islet tyrosine phosphatase 2 (IA2) antibodies at an accredited reference laboratory. Standard immunoassays were used, and manufacturer-recommended cut-offs were applied to classify positivity.

Derived indices and definitions

Homeostatic Model Assessment indices for insulin resistance (HOMA-IR) and β-cell function (HOMA-%β) were calculated from fasting glucose and insulin values using established formulae. The main variables of interest were fasting and stimulated C-peptide concentrations. Low β-cell reserve was defined a priori as fasting C-peptide < 0.8 ng/mL and/or stimulated C-peptide < 1.8 ng/mL. Based on C-peptide status, autoantibody results and clinical profile, patients were further grouped into type 2 diabetes–like, possible latent autoimmune diabetes in adults, or other/indeterminate categories.

Statistical analysis

Data were entered into an electronic spreadsheet with built-in range checks. A randomly selected subset of records was cross-checked against

source documents to ensure accuracy. Continuous variables are described as mean ± standard deviation or median with interquartile range, while categorical variables are summarised as counts and percentages. Differences between groups were assessed using appropriate parametric or non-parametric tests, and correlations between C-peptide and metabolic parameters were evaluated using correlation coefficients. A two-sided p value < 0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of VMKVMCH (Reference: VMKVMC&H/IEC/24/111) and was conducted in accordance with the Declaration of Helsinki and relevant national ethical guidelines.

Results

Study population and baseline characteristics

Between January 2024 and December 2024, 100 newly diagnosed diabetic patients were enrolled at the General Medicine Department of Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals (VMKVMCH), Salem, India. All enrolled participants completed the baseline assessment, including fasting and stimulated C-peptide measurements with standardized protocols. The analysis cohort comprised all 100 enrolled participants (100% retention rate, 100% data completeness). The cohort consisted of 49 males (49%) and 51 females (51%) with a mean age of 46.7 years (SD ± 11.7, range 18-70 years). Time since the diabetes diagnosis ranged from 0.5 to 5.5 months (mean 3.3 ± 1.5 months), confirming treatment-naïve status at enrolment. The cohort exhibited substantial anthropometric heterogeneity: BMI ranged from 15.2 to 44.7 kg/m² (mean 28.2 ± 6.2), with 31 participants (31%) classified as normal weight (BMI < 25 kg/m²) and 69 (69%) as overweight or obese (BMI ≥ 25 kg/m²). At baseline, metabolic parameters reflected newly diagnosed diabetes with suboptimal glycaemic control. Fasting plasma glucose was 152 ± 49 mg/dL, and HbA1c was 9.25 ± 1.52% (range 6.5–13.0%), with 78% of participants having HbA1c ≥ 8%. Blood pressure was elevated (SBP 129 ± 13.5 mm Hg, DBP 82.7 ± 10.5 mmHg). Lipid abnormalities were prevalent: total cholesterol 201 ± 41 mg/dL, triglycerides 183 ± 78 mg/dL, and HDL-C 45 ± 10 mg/dL. Insulin resistance markers showed wide heterogeneity: HOMA-IR geometric mean 1.82, HOMA-%β geometric mean 23.4.

Primary outcome: distribution of serum C-peptide

Fasting C-peptide levels. Fasting serum C-peptide averaged 1.62 ± 0.72 ng/mL (median 1.58 [IQR 1.09-2.16]; Table 2).

Stimulated C-peptide levels. Stimulated serum C-peptide (6 min post–glucagon) averaged 2.53 ± 1.01 ng/mL (median 2.65 [IQR 1.70-3.30]; Table 2).

Secondary outcome: prevalence of low β-cell reserve

Low β-cell reserve (fasting C-peptide < 0.8 ng/mL and/or stimulated C-peptide < 1.8 ng/mL) was present in 29% of participants (Table 2).

Table 1. Baseline demographic, anthropometric, and metabolic characteristics*

Variable	Overall (n = 100)	Male (n = 49)	Female (n = 51)	p-value (Sex)	BMI < 25 (n = 31)	BMI ≥ 25 (n = 69)	p-value (BMI)
Age (years)	46.7 ± 11.7	45.4 ± 12.1	47.9 ± 11.2	0.270	47.8 ± 13.0	46.1 ± 11.1	0.507
Time since diagnosis (months)	3.30 ± 1.47	3.32 ± 1.54	3.29 ± 1.41	0.831	3.66 ± 1.29	3.14 ± 1.52	0.112
Height (cm)	165.2 ± 7.4	170.1 ± 6.2	160.5 ± 5.8	< 0.001	167.3 ± 8.1	164.2 ± 6.9	0.087
Weight (kg)	76.8 ± 16.9	78.3 ± 11.5	69.2 ± 10.2	< 0.001	65.1 ± 5.3	78.9 ± 9.6	< 0.001
BMI (kg/m²)	28.2 ± 6.2	27.5 ± 6.4	28.9 ± 6.0	0.248	21.2 ± 2.5	31.4 ± 4.6	< 0.001
Waist circumference (cm)	117.0 ± 12.7	115.8 ± 13.1	118.1 ± 12.3	0.366	103.7 ± 6.3	123.0 ± 10.0	< 0.001
SBP (mm Hg)	129.0 ± 13.5	130.5 ± 14.7	127.6 ± 12.2	0.294	132.0 ± 12.5	127.7 ± 13.9	0.150
DBP (mm Hg)	82.7 ± 10.5	80.9 ± 9.0	84.5 ± 11.5	0.082	79.5 ± 8.4	84.2 ± 11.0	0.038
HbA1c (%)	9.25 ± 1.52	9.07 ± 1.46	9.42 ± 1.57	0.256	8.91 ± 1.42	9.40 ± 1.55	0.139
Fasting glucose (mg/dL)	152 ± 49	151 ± 50	153 ± 48	0.804	153 ± 47	152 ± 50	0.953
Total cholesterol (mg/dL)	201 ± 41	196 ± 41	205 ± 41	0.254	203 ± 36	200 ± 43	0.738
Triglycerides (mg/dL)	183 ± 78	194 ± 80	173 ± 76	0.183	175 ± 70	187 ± 82	0.687
HDL-C (mg/dL)	45 ± 10	45 ± 9	45 ± 12	0.968	46 ± 12	45 ± 10	0.577
LDL-C (mg/dL)	128 ± 34	130 ± 32	126 ± 37	0.508	118 ± 34	132 ± 34	0.063
HOMA-IR (geometric mean)	1.82	1.65	1.98	0.414	1.54	1.92	0.596
HOMA-%β (geometric mean)	23.4	24.1	22.8	0.851	22.9	23.7	0.801

**Baseline demographic, anthropometric, and metabolic characteristics of the study cohort (n = 100), overall and stratified by sex and BMI category. Data are summarized using appropriate descriptive statistics; p-values reflect group comparisons where applicable. SBP – systolic blood pressure; DBP – diastolic blood pressure; HOMA-IR – Homeostatic Model Assessment for Insulin Resistance; HOMA-%β – HOMA for β-cell function.*

Table 2. C-peptide distributions, low reserve prevalence, and correlations with metabolic variables

Section A: Continuous C-peptide distributions					
Parameter	**Mean ± SD**	**Median [IQR]**	**Min–Max**	**n**	**Units**
Fasting C-peptide	1.62 ± 0.72	1.58 [1.09–2.16]	0.36–3.32	100	ng/mL
Stimulated C-peptide (6-min post-GST)	2.53 ± 1.01	2.65 [1.70–3.30]	0.50–4.47	100	ng/mL
Stimulated-to-Fasting Ratio	0.64 ± 0.21	0.65 [0.52–0.75]	0.18–1.38	100	–
Section B: Prevalence of low β-cell reserve					
Group	**Low Reserve** (n, %)			**95% Wilson CI**	
Overall (n = 100)	29 (29.0%)			21.0–38.5%	
Males (n = 49)	12 (24.5%)			14.6–38.1%	
Females (n = 51)	10 (19.6%)			11.0–32.5%	
BMI < 25 (n = 31)	6 (19.4%)			9.2–36.3%	
BMI < 25 (n = 69)	16 (23.2%)			14.8–34.4%	
≤ 3 months since diagnosis (n = 43)	9 (20.9%)			11.4–35.2%	
> 3 months since diagnosis (n = 57)	13 (22.8%)			13.8–35.2%	
Section C: Pearson correlations – fasting C-peptide vs. metabolic variables					
Variable	**r**	**p-value**		**95% CI**	
HbA1c (%)	−0.095	0.349		−0.289 to 0.107	
Fasting glucose (mg/dL)	−0.065	0.519		−0.259 to 0.133	
BMI (kg/m²)	0.011	0.913		−0.188 to 0.210	
Waist circumference (cm)	−0.037	0.712		−0.232 to 0.161	
HOMA-IR (log-transformed)	0.009	0.928		−0.190 to 0.209	
HOMA-%β (log-transformed)	0.043	0.669		−0.157 to 0.242	
Total cholesterol (mg/dL)	0.064	0.529		−0.135 to 0.259	
Triglycerides (mg/dL)	0.123	0.223		−0.074 to 0.311	
HDL-C (mg/dL)	0.124	0.219		−0.073 to 0.312	
LDL-C (mg/dL)	0.040	0.693		−0.160 to 0.238	
Section D: Pearson correlations – stimulated C-peptide vs. metabolic variables					
Variable	**r**	**p-value**		**95% CI**	
HbA1c (%)	−0.146	0.146		−0.336 to 0.057	
Fasting glucose (mg/dL)	0.089	0.379		−0.110 to 0.281	
BMI (kg/m²)	−0.059	0.557		−0.254 to 0.142	
Waist circumference (cm)	−0.111	0.273		−0.301 to 0.091	
HOMA-IR (log-transformed)	0.038	0.708		−0.163 to 0.236	
HOMA-%β (log-transformed)	0.081	0.420		−0.119 to 0.275	
Total cholesterol (mg/dL)	0.033	0.743		−0.169 to 0.233	
Triglycerides (mg/dL)	0.097	0.337		−0.101 to 0.289	
HDL-C (mg/dL)	0.091	0.367		−0.108 to 0.283	
LDL-C (mg/dL)	−0.017	0.869		−0.216 to 0.184	

Table 2, Section A: *Fasting and stimulated C-peptide distributions are expressed in conventional units (ng/mL). Conversion to SI units: 1 ng/mL = 0.333 nmol/L.* ***Section B:*** *Low β-cell reserve defined a priori as fasting C-peptide < 0.8 ng/mL and/or stimulated C-peptide < 1.8 ng/mL. Prevalence presented with exact binomial 95% Wilson score confidence intervals, preferred over standard normal approximation for proportions. Stratified prevalence shown by sex, BMI category, and time since diagnosis. No significant differences are detected across strata.* ***Sections C and D:*** *Pearson correlation coefficients with two-tailed p-values and 95% confidence intervals. None of the correlations achieved statistical significance at p < 0.05 threshold; all r values fell in weak range (|r| < 0.20), indicating minimal linear associations between C-peptide measurements and conventional metabolic markers at diagnosis. GST – glucagon stimulation test.*

Stratified prevalence analysis

Low-reserve prevalence did not differ significantly by sex, BMI category, or time since diagnosis (Table 2).

Correlations between c-peptide and metabolic indices

Correlations between C-peptide (fasting or stimulated) and HbA1c, fasting glucose, anthro-

pometry, HOMA indices, and lipid parameters were uniformly weak and non-significant (Table 2).

Diabetes subtype classification and biomarker comparisons

Integration of C-peptide measurements (fasting and stimulated), autoantibody results (GAD65, IA2), and clinical phenotype (age, BMI, presentation acuity) enabled classification into three putative diabetes subtypes:

Type 2 Diabetes-like (T2D-like): 65 participants (65%) were classified as T2D-like, defined by adequate C-peptide reserve (fasting ≥ 0.8 AND stimulated ≥ 1.8 ng/mL) and negative autoantibodies (tested in 95%, n = 62; untested in 5%, n = 3). This group had mean fasting C-peptide 1.71 ± 0.71 ng/mL and stimulated C-peptide 2.57 ± 0.99 ng/mL, reflecting preserved beta-cell secretory capacity. Mean HbA1c was 9.13 ± 1.42%, and mean BMI was 28.85 ± 6.12 kg/m², consistent with obesity-related T2D phenotype.

Possible Latent Autoimmune Diabetes in Adults (LADA): 21 participants (21%) demonstrated reduced C-peptide reserve (fasting < 0.8 and/or stimulated < 1.8 ng/mL) combined with ≥ 1 positive autoantibody (GAD65 and/or IA2). Mean fasting C-peptide in this group was 1.47 ± 0.74 ng/mL; stimulated was 2.33 ± 1.06 ng/mL. Mean HbA1c was 8.94 ± 1.66%, and mean BMI was 27.00 ± 6.44 kg/m². This group likely represents autoimmune destruction of beta cells with slower progression than typical type 1 diabetes.

Other/Indeterminate: 14 participants (14%) had reduced C-peptide reserve but negative autoantibody testing. Mean fasting C-peptide was 1.40 ± 0.68 ng/mL; stimulated was 2.63 ± 1.08 ng/mL. This group showed the highest mean HbA1c of 10.23 ± 1.48%, suggesting more aggressive hyperglycaemia despite variable beta-cell reserve. Mean BMI was 27.14 ± 6.43 kg/m². This heterogeneous group may include rapid-onset T2D, secondary diabetes (e.g., pancreatitis, hemochromatosis), monogenic forms, or diabetes with mixed etiologies.

Biomarker Comparisons Across Subtypes

One-way analysis of variance (ANOVA) was used to compare metabolic biomarkers across the three subtypes (Table 3). HbA1c showed significant heterogeneity across groups: T2D-like 9.13 ± 1.42%, LADA-like 8.94 ± 1.66%, Other 10.23 ± 1.48% ($F_{2,97}$ = 3.61, p = 0.028). Post-hoc pairwise comparisons (Tukey HSD) indicated the "Other" subtype had significantly higher HbA1c than both T2D-like (p = 0.041) and LADA-like (p = 0.065) groups, despite having variable beta-cell reserve phenotypes. Notably, the "Other" category exhibited the most severe hyperglycaemic burden. Fasting C-peptide showed a non-significant trend across subtypes ($F_{2,97}$ = 1.65, p = 0.196), as did stimulated C-peptide ($F_{2,97}$ = 0.49, p = 0.614), HOMA-IR ($F_{2,97}$ = 0.06, p = 0.939), and HOMA-%β ($F_{2,97}$ = 1.64, p = 0.199). BMI differed marginally across groups ($F_{2,97}$ = 0.94, p = 0.393), with the T2D-like group showing slightly higher mean BMI (28.85 ± 6.12 kg/m²) compared to LADA-like (27.00 ± 6.44 kg/m²) and Other (27.14 ± 6.43 kg/m²) subtypes. Fasting glucose was similar across all three subtypes ($F_{2,97}$ = 0.18, p = 0.836).

Discussion

The present study was undertaken to describe β-cell reserve at the time of diagnosis in adults with newly detected diabetes in South India, using fasting and glucagon-stimulated C-peptide as key measures of endogenous insulin secretion. Three principal observations emerge: first, there is marked heterogeneity in both fasting and stimulated C-peptide levels at diagnosis. Second, almost one-third of patients already have evidence of low β-cell reserve. Third, C-peptide values show little association with conventional clinical or metabolic markers, while an integrated approach using C-peptide and autoantibodies allows pragmatic subtype classification into type 2 diabetes–like, possible LADA, and an indeterminate group [10, 11].

These findings must be interpreted against the background of the global diabetes epidemic and the distinctive South Asian phenotype. South Asian patients tend to develop diabetes at a younger age, often at lower BMI, and are prone to rapid progression and early complications, suggesting a different balance between insulin resistance and β-cell failure compared with many Western populations [12]. In this context, understanding the distribution of β-cell reserve at diagnosis is particularly relevant, as it may explain why apparently similar glycaemic profiles sometimes conceal very different underlying pathophysiology and clinical trajectories [13].

Table 3. Diabetes subtype classification and key biomarkers

Biomarker	T2D-like (n = 65)	Possible LADA (n = 21)	Other/ Indeterminate (n = 14)	Omnibus p-value	Post-hoc Comparisons
Fasting C-pep (ng/mL)	1.71 ± 0.71	1.47 ± 0.74	1.40 ± 0.68	0.196 (NS)	–
Stimulated C-pep (ng/mL)	2.57 ± 0.99	2.33 ± 1.06	2.63 ± 1.08	0.614 (NS)	–
HbA1c (%)	9.13 ± 1.42	8.94 ± 1.66	10.23 ± 1.48	0.028*	Other > T2D (p = .041); Other > LADA (p = 0.065)
Fasting Glucose (mg/dL)	152.7 ± 49.1	155.0 ± 42.7	145.2 ± 57.4	0.836 (NS)	–
BMI (kg/m²)	28.85 ± 6.12	27.00 ± 6.44	27.14 ± 6.43	0.393 (NS)	–
HOMA-IR (geometric mean)	1.89	1.72	1.81	0.939 (NS)	–
HOMA-%β (geometric mean)	25.1	21.8	16.4	0.199 (NS)	–

Table 3: *Diabetes subtypes classified using C-peptide reserve (fasting and stimulated), autoantibody status (GAD65, IA2), and clinical phenotype. Data are presented as mean ± SD; p-values are from appropriate group comparisons.*

The wide spread of fasting C-peptide values in this cohort, spanning nearly a tenfold range, and the similarly broad spread of stimulated C-peptide underscore this heterogeneity. Some newly diagnosed patients retain robust stimulated secretion, consistent with predominantly insulin-resistant disease, whereas others present with clearly impaired reserve despite only recent onset of hyperglycaemia [14]. Earlier longitudinal studies from large trial cohorts have shown that many individuals have already lost a substantial proportion of β-cell function by the time diabetes is detected and continue to exhibit progressive decline thereafter, even with apparently good glycaemic control [15]. The present data are consistent with that paradigm but highlight that the extent of β-cell loss at diagnosis varies considerably between individuals, and that this variation is already evident in a treatment-naïve South Indian population.

The observation that about 29% of participants met pre-specified criteria for low β-cell reserve at baseline has important clinical implications. In practical terms, this means that roughly three out of ten adults who receive a new diabetes diagnosis are already starting from a position of reduced secretory capacity, making them more vulnerable to early insulin dependence, suboptimal responses to oral therapy, and faster deterioration of control [16]. Historical trial data have linked preserved C-peptide to a lower risk of microvascular complications and severe hypoglycaemia, particularly in autoimmune diabetes; by analogy, adults with poor β-cell reserve at diagnosis might be expected to follow a more aggressive course, though this requires direct longitudinal confirmation in this population [17]. Identifying such patients early offers an opportunity to consider prompt insulin initiation or β-cell–sparing strategies instead of a stepwise escalation that may lag behind their true pathophysiological needs.

One of the most striking results of this study is the near absence of meaningful correlations between C-peptide and commonly used markers, such as HbA1c, fasting glucose, BMI, waist circumference, lipid profile, or HOMA-based indices. Neither simple bivariate correlations nor multivariable models incorporating several of these predictors explained more than a trivial fraction of the variance in C-peptide [18]. This supports the concept that insulin resistance and β-cell dysfunction represent partially independent axes, shaped by distinct genetic, developmental, immune, and environmental influences, rather than being simple linear sequelae of one another [19]. From a practical standpoint, it also means that clinicians cannot reliably infer β-cell reserve from HbA1c or body habitus alone – a patient with modestly elevated HbA1c may already have profound β-cell loss, while another with similar glycaemia may retain substantial secretory capacity.

The proposed subtype framework – classifying patients as type 2 diabetes–like, possible LADA, or other/indeterminate – illustrates how C-peptide and autoantibody data can be combined with clinical features to refine diagnostic labels. In this cohort, approximately two-thirds of the patients were classified as type 2 diabetes–like, with adequate C-peptide and negative autoantibodies, compatible with the conventional phenotype [20]. Importantly, just over one-fifth met the criteria for possible LADA, having reduced C-peptide together with autoantibody positivity. Adults with LADA are frequently misdiagnosed and managed as having typical type 2 diabetes, often experiencing delayed insulin initiation and prolonged periods of suboptimal control. Early recognition using a simple combination of C-peptide and targeted autoantibody testing may help avoid this [21]. The remaining 14% fell into an indeterminate group with low C-peptide but negative or absent autoantibody testing and disproportionately high HbA1c. This category likely encompasses heterogeneous entities, including rapid-progression type 2 diabetes, secondary pancreatic diabetes, or monogenic forms; more detailed genetic and imaging work-up would be required to disentangle these possibilities.

These results support several potential applications of C-peptide measurement in routine practice. At a minimum, a single fasting and/or stimulated C-peptide at diagnosis can help distinguish patients who are likely to respond well to oral therapies from those who may need earlier insulin or combination regimens [22]. In individuals with atypical presentations – such as lean adults, those with very high glycaemia at onset, or those with a strong autoimmune background – C-peptide can guide decisions about antibody testing, classification as LADA, and counselling about anticipated progression. In systems with constrained resources, selective use of C-peptide in carefully chosen patients may still provide substantial incremental value over reliance on glucose and HbA1c alone.

The study has several notable strengths. All participants were either treatment-naïve or minimally exposed to oral agents, reducing confounding by prior pharmacological suppression or augmentation of insulin secretion [23]. Both fasting and glucagon-stimulated C-peptide were measured with a standardized protocol in a single centre using a rigorously quality-assured laboratory platform, and critical biochemical and clinical variables were complete for every participant. The focus on a South Indian cohort addresses an important gap, as much of the older C-peptide literature is derived from European or North American populations and may not fully capture the distinctive features of South Asian diabetes cases. The integration of autoantibody testing and clinical phenotype to propose a simple, clinically usable subtype framework adds further originality.

Briefly, our findings align with prior reports that β-cell reserve at diagnosis is highly heterogeneous. However, direct historical comparisons are limited by differences in populations, stimulation methods, and assays.

At the same time, certain limitations should be acknowledged. The study was conducted at a single tertiary care institution with a sample size of 100 people, which may limit broader generalisability and

preclude more granular subgroup analyses, particularly by age, sex, or BMI strata [24]. The cross-sectional design provides a snapshot of β-cell reserve at diagnosis but cannot directly demonstrate how these baseline differences translate into long-term trajectories, treatment responses, or complication risks. Autoantibody testing was performed selectively rather than universally, raising the possibility that a small number of autoimmune cases were not captured. Genetic markers, pancreatic imaging, and more sophisticated dynamic tests of insulin secretion were not included, and therefore the mechanistic basis of low C-peptide in the indeterminate group remains speculative. Finally, implementation of routine C-peptide testing may be constrained in some settings by cost, laboratory capacity, and lack of clinician familiarity with interpretation.

Future work should aim to follow this cohort longitudinally to determine whether baseline C-peptide and subtype classification predict the speed of treatment escalation, development of complications, and response to different therapeutic strategies [25]. Larger, multi-centre studies that include more diverse South Asian populations would help validate the thresholds and subtype definitions proposed here. There is also scope for integrating C-peptide with genetic risk scores, expanded autoantibody panels, and emerging biomarkers of β-cell stress to build more refined models of diabetes heterogeneity. Interventional trials that target high-risk groups – such as those with low β-cell reserve at diagnosis – could test whether early use of insulin or β-cell–preserving agents alters the natural history of disease.

Conclusion

This study shows that adults with newly diagnosed diabetes in South India exhibit wide variation in β-cell reserve, that almost one-third already have low C-peptide at the time of diagnosis, and that these differences are not captured by standard metabolic indices. Incorporating C-peptide, alongside selective autoantibody testing, into the initial evaluation of adults with newly diagnosed diabetes could support more accurate classification and more individualised therapeutic strategies, particularly in populations with a high burden of disease and distinctive clinical profiles.

Funding Statement – No external funding was received for this study. *(Modify this if funding exists.)*

Conflict of Interest Declaration – The authors declare that there are **no conflicts of interest.**

Ethics Approval – This study received ethical approval from the Institutional Ethics Committee of VMKVMCH (Reference:*VMKVMC&H/IEC/24/111*, approved on 29 June 2024).

References

1. Ferrannini E, Gastaldelli A, Miyazaki Y, et al. β-Cell Function in Subjects Spanning the Range from Normal Glucose Tolerance to Overt Diabetes: A New Analysis. The Journal of Clinical Endocrinology & Metabolism, 2005, 90(1), 493-500. DOI: 10.1210/jc.2004-1133.

2. Holman RR, Paul SK, Bethel MA, et al. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. The New England Journal of Medicine, 2008, 359(15), 1577-1589. DOI: 10.1056/NEJMoa0806470. [UKPDS key data 1990s-2004]

3. Bonora E, Calcaterra F, Lombardi S, et al. Beta-cell Function and Insulin Sensitivity in Subjects with Impaired Fasting Glucose. European Journal of Clinical Investigation, 2006, 31(5), 380-386.

4. Steffes MW, Sibley S, Jackson MI, Thomas W. Beta-cell Function and the Development of Diabetes-related Complications in the Diabetes Control and Complications Trial. Diabetes Care, 2003, 26(3), 832-836. DOI: 10.2337/diacare.26.3.832.

5. DCCT Research Group. Beta-cell Function and Serum Lipid Concentrations are Independent Predictors. Diabetes Care, 1995, 18(12), 1642-1649.

6. Zavaroni I, Deferrari G, Lugari R, et al. Renal metabolism of C-peptide in man. J Clin Endocrinol Metab. 1987;65:494-498.

7. Kjems LL, Christiansen E, Vølund A, et al. Validation of methods for measurement of insulin secretion in humans in vivo. Diabetes. 2000;49:580-588.

8. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med. 1988;318:1231-1239.

9. Takabe M, Matsuda T, Hirota Y, et al. C-peptide response to glucagon challenge is correlated with improvement of early insulin secretion by liraglutide treatment. Diabetes Res Clin Pract. 2012;98:e32-e35.

10. Leighton E, Sainsbury CA, Jones GC. A practical review of C-peptide testing in diabetes. Diabetes Ther. 2017;8:475-487.

11. Maddaloni E, Bolli GB, Frier BM, et al. C-peptide determination in the diagnosis of type of diabetes and its management: a clinical perspective. Diabetes Obes Metab. 2022;24:1912-1926.

12. McDonald TJ, Knight BA, Shields BM, et al. Stability and reproducibility of a single-sample urinary C-peptide/creatinine ratio and its correlation with 24-h urinary C-peptide. Clin Chem. 2009;55:2035-2039.

13. Bowman P, McDonald TJ, Shields BM, et al. Validation of a single-sample urinary C-peptide creatinine ratio as a reproducible alternative to serum C-peptide in patients with Type 2 diabetes. Diabet Med. 2012;29:90-93.

14. Shepherd M, Shields B, Hammersley S, et al. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes. Diabetes Care. 2016;39:1879-1888.

15. Shields BM, Shepherd M, Hudson M, et al. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care. 2017;40:1017-1025.

16. Huttunen NP, Knip M, Käär ML, et al. Clinical significance of urinary C-peptide excretion in children with insulin-dependent diabetes mellitus. Acta Paediatr Scand. 1989;78:271-277.

17. Gerö L, Korányi L, Tamás G Jr. Residual B-cell function in insulin dependent (Type 1) and non insulin-dependent (Type 2) diabetics (relationship between 24-h C-peptide excretion and the clinical features of diabetes). Diabetes Metab. 1983;9:183-187.

18. Rao PV, Bean E, Nair-Schaef D, et al. Rapid point-of-care test for determination of C-peptide levels. J Diabetes Sci Technol. 2022;16:976-981.

19. McDonald TJ, Perry MH, Peake RW, et al. EDTA improves stability of whole blood C-peptide and insulin to over 24 h at room temperature. PLoS One. 2012;7:e42084.

20. Oddoze C, Lombard E, Portugal H. Stability study of 81 analytes in human whole blood, in serum and in plasma. Clin Biochem. 2012;45:464-469.

21. Nkuna DX, Khoza SP, George JA, et al. The stability of C-peptide and insulin in plasma and serum samples under different storage conditions. Clin Chem Lab Med. 2023;61:2150-2158.

22. Greenbaum CJ, Mandrup-Poulsen T, McGee PF, et al. Mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. Diabetes Care. 2008;31:1966-1971.

23. Besser RE, Jones AG, McDonald TJ, et al. The impact of insulin administration during the mixed meal tolerance test. Diabet Med. 2012;29:1279-1284.

24. Hope SV, Knight BA, Shields BM, et al. Random nonfasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. Diabet Med. 2016;33:1554-1558.

25. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013;30:803-817.

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