International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Observational Evaluation of Immune Biomarkers, Residual C Peptide, and Metabolic Control in Individuals with Type 1 Diabetes Receiving Gene Based or Cell Replacement Interventions

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Received: 20-01-2026
Accepted: 21-02-2026
Available online: 24-02-2026

ABSTRACT

Background: Gene-based and cell-replacement approaches aim to restore endogenous insulin secretion in type 1 diabetes, yet clinical responses are heterogeneous and may depend to residual β-cell function and immune-inflammatory status.

Objectives: To describe baseline immune biomarker patterns and residual C-peptide status, and to evaluate short-term changes in glycemic control and insulin requirements among individuals receiving gene-based or cell-replacement interventions in routine care.

Methods: This single-centre 6-month observational study enrolled 100 individuals with type 1 diabetes at a tertiary care centre in Telangana, India (May–October 2025). Baseline demographics, diabetes history, HbA1c, fasting glucose, insulin dose, residual C-peptide, and inflammatory biomarkers (hs-CRP, IL-6, TNF-α, IL-10/IL-6 ratio) were recorded. Follow-up assessment at endpoint included HbA1c, fasting glucose, insulin dose, and time-in-range in continuous glucose monitoring users.

Results: Among 100 participants (mean age 24.8 years, baseline HbA1c 8.6%), 46% had detectable C-peptide. At 6-month, mean HbA1c decreased to 7.7%, fasting glucose declined by 22mg/dL, and daily insulin dose decreased by 0.12U/kg/day. Time-in-range improved in continuous glucose monitoring users. Greater HbA1c and insulin-dose reductions were observed in those with detectable C-peptide and in the cell-replacement subgroup. Insulin independence was achieved by 6% of participants, and severe hypoglycemia continued to occur during follow-up.

Conclusion: In this observational cohort, improved metabolic control after advanced interventions was accompanied by reduced insulin needs, with more favourable changes among participants retaining measurable C-peptide. Baseline inflammatory activation was common, supporting combined metabolic and immune monitoring when evaluating emerging therapies.

Keywords: *Type 1 diabetes; C-peptide; Inflammatory biomarkers; Gene therapy; Cell replacement; Time in range*

Introduction

Type 1 diabetes is characterized by immune-mediated β-cell destruction, leading to lifelong insulin dependence and risk of acute and chronic complications. Despite advances in insulin formulations, delivery devices, and glucose sensing, many individuals still experience glycemic variability, hypoglycemia, and progressive microvascular risk, especially when target HbA1c levels are not sustained [1]. Long-term evidence from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up established that improved glycemic control reduces microvascular outcomes. However, intensive strategies carry a higher hypoglycemia burden and require durable behavioral and technological support [1].

Residual β-cell function, commonly assessed by fasting or stimulated C-peptide, remains clinically meaningful even in established disease. DCCT analyses demonstrated that preserved C-peptide is associated with lower HbA1c, reduced insulin requirements, and fewer severe hypoglycemia events, while also correlating with microvascular risk trajectories [2–4]. Methodological guidance from an American Diabetes Association workshop supports C-peptide as an appropriate endpoint for interventions that aim to preserve or restore endogenous insulin secretion [5]. In parallel, continuous glucose monitoring (CGM) metrics, particularly time-in-range (70–180 mg/dL), have emerged as patient-centered measures that complement HbA1c and capture clinically relevant glycemic exposure [6].

Therapies that seek to re-establish insulin production include cell-based replacement (e.g., islet transplantation or stem cell-derived β-cell products) and gene-based strategies that seek to protect β-cells, reprogram non-β cells toward insulin secretion, or modulate autoimmunity. Clinical islet transplantation has shown the capacity to improve glycemic stability and reduce severe hypoglycemia, though insulin independence can wane over time and is constrained by donor availability and immunosuppression [7,8]. Recent reviews highlight efforts to expand scalable cell sources and improve engraftment, while gene-based approaches continue to evolve across preclinical and translational stages [9–11,14].

Inflammation is increasingly recognized as a modifier of metabolic outcomes in type 1 diabetes. Elevated inflammatory markers can reflect intercurrent stress, adiposity, and immune activation, and have been linked to glycemic control and vascular risk in several cohorts [12,13]. These observations highlight the need to interpret clinical metabolic responses to emerging interventions within a broader immune-inflammatory context.

The objectives of this study were to (i) describe baseline immune biomarker patterns and residual C-peptide status among individuals with type 1 diabetes receiving gene-based or cell-replacement interventions, and (ii) evaluate short-term changes in metabolic control and insulin requirements over a 6-month follow-up period.

Materials and Methods

Study design and setting: This single-centre observational cohort documented clinical and laboratory changes in individuals with type 1 diabetes receiving advanced therapies during routine care at Prathima Institute of Medical Sciences

(PIMS), Karimnagar, Telangana, India. Baseline evaluation was completed at enrolment and the endpoint visit was scheduled at 6 months (±2 weeks).

Participants and sampling: Consecutive clinic attendees were screened. Inclusion criteria were confirmed type 1 diabetes, age ≥12 years, on insulin therapy, and receipt of either a gene-based therapeutic intervention or a cell-replacement intervention during the study period. Exclusion criteria included acute systemic infection at enrolment, pregnancy, advanced kidney failure requiring dialysis, or inability to complete follow-up. Written informed consent (and assent where applicable) was obtained. A total of 100 participants were enrolled.

Exposure classification: Participants were classified by primary intervention received: gene-based interventions (intended to modulate immunity and/or enhance insulin production using gene delivery or gene-modified cells) or cell-replacement interventions (delivery of insulin-producing cells, including islet-based or stem cell-derived products) [7–11,14]. Allocation was not randomized; therapies were delivered according to treating team decisions and protocol eligibility.

Clinical and laboratory measurements: A structured proforma captured age, sex, diabetes duration, history of severe hypoglycemia and diabetic ketoacidosis in the preceding year, fasting plasma glucose, HbA1c, and total daily insulin dose (U/kg/day). Residual β-cell function was assessed by fasting serum C-peptide and categorized as detectable (≥0.10 ng/mL) or undetectable, aligned with interpretive guidance for C-peptide reporting [3,5]. Immune-inflammatory biomarkers (hs-CRP, IL-6, TNF-α, and IL-10/IL-6 ratio) were measured from fasting samples using standardized immunoassays with internal quality checks. At endpoint, HbA1c, fasting glucose, and insulin dose were re-measured. CGM-derived time-in-range (70–180 mg/dL) was extracted for participants who used CGM for at least 14 days with ≥70% active data, consistent with consensus recommendations [6].

Definitions and outcomes: Primary outcomes were changes in HbA1c, fasting plasma glucose, and insulin dose from baseline to endpoint. Secondary outcomes included HbA1c reduction ≥1%, HbA1c <7% at endpoint, ≥50% insulin-dose reduction, and complete insulin independence at endpoint. Severe hypoglycemia was defined as an episode requiring external assistance for recovery [1,3].

Statistical analysis: Continuous variables are presented as mean ± SD and categorical variables as n (%). Changes from baseline to endpoint are summarized as mean differences. Stratified analyses were performed by residual C-peptide category and by intervention type. Findings were interpreted descriptively given the observational design.

Ethical considerations: The protocol received approval from the Institutional Ethics Committee of PIMS. Participant confidentiality was maintained through de-identification and restricted access to study records.

Results

Baseline demographic and clinical features are summarized in Table 1. The cohort had a mean age of 24.8 ± 9.6 years, and 58% were male. Diabetes duration was <5 years in 34%, 5–10 years in 41%, and >10 years in 25%. Baseline HbA1c averaged 8.6 ± 1.4% and fasting plasma glucose 176 ± 48 mg/dL. Detectable fasting C-peptide (≥0.10 ng/mL) was present in 46% of participants.

Table 1. Baseline Demographic and Clinical Characteristics (N = 100)

Variable	Value
Age (years), mean ± SD	24.8 ± 9.6
Male, n (%)	58 (58%)
Female, n (%)	42 (42%)
Duration of diabetes <5 years, n (%)	34 (34%)
Duration 5–10 years, n (%)	41 (41%)
Duration >10 years, n (%)	25 (25%)
Baseline HbA1c (%), mean ± SD	8.6 ± 1.4
Fasting plasma glucose (mg/dL), mean ± SD	176 ± 48
Total daily insulin dose (U/kg/day), mean ± SD	0.62 ± 0.18
History of severe hypoglycemia (past year), n (%)	36 (36%)
Diabetic ketoacidosis (past year), n (%)	18 (18%)
Detectable C-peptide (≥0.10 ng/mL), n (%)	46 (46%)
Undetectable C-peptide, n (%)	54 (54%)

Baseline immune-inflammatory biomarkers are shown in Table 2. Elevated hs-CRP (>3 mg/L) was observed in 38%, IL-6 (>4 pg/mL) in 34%, and TNF-α (>8 pg/mL) in 29%. A high inflammatory state (≥2 elevated markers) was identified in 27% of participants, while an IL-10/IL-6 ratio >1 was present in 22%.

Table 2. Immune Biomarker Profile at Baseline

Biomarker	Elevated, n (%)
hs-CRP >3 mg/L	38 (38%)
IL-6 >4 pg/mL	34 (34%)
TNF-α >8 pg/mL	29 (29%)
High inflammatory state (≥2 elevated markers)	27 (27%)
IL-10/IL-6 ratio >1	22 (22%)

Changes in metabolic parameters at endpoint are presented in Table 3. Mean HbA1c decreased from 8.6 ± 1.4% at baseline to 7.7 ± 1.3% at endpoint (mean change −0.9%). Fasting plasma glucose declined by 22 mg/dL, and total daily insulin dose decreased by 0.12 U/kg/day. Among 72 participants with CGM data meeting wear-time criteria, time-in-range increased by 11 percentage points. An HbA1c reduction ≥1% was achieved by 48 participants (48%), and 6 (6%) attained complete insulin independence at the endpoint.

Table 3. Changes in Metabolic Parameters at Endpoint

Parameter	Baseline	Endpoint	Mean change
HbA1c (%)	8.6 ± 1.4	7.7 ± 1.3	−0.9
Fasting plasma glucose (mg/dL)	176 ± 48	154 ± 44	−22
Insulin dose (U/kg/day)	0.62 ± 0.18	0.50 ± 0.17	−0.12
Time-in-range (%)	52 ± 14	63 ± 15	+11
HbA1c reduction ≥1%, n (%)	—	48 (48%)	—
Complete insulin independence, n (%)	—	6 (6%)	—

*Time-in-range was available in 72 participants using continuous glucose monitoring.

Outcomes stratified by residual C-peptide and intervention type are shown in Table 4. Participants with detectable C-peptide demonstrated greater HbA1c reduction (−1.2 ± 0.8% vs −0.6 ± 0.7%) and larger insulin-dose reduction (−0.18 ± 0.11 vs −0.08 ± 0.10 U/kg/day) compared with those with undetectable C-peptide. The cell-replacement subgroup showed slightly greater mean HbA1c and insulin-dose reductions than the gene-based subgroup. Severe hypoglycemia during follow-up occurred more often in the undetectable C-peptide group (22% vs 13%). Intervention-specific documentation of severe hypoglycemia was complete for the gene-based subgroup (18%) but incomplete for the cell-replacement subgroup.

Table 4. Outcomes Stratified by Residual C-Peptide and Intervention Type

Outcome	Detectable C-peptide (n=46)	Undetectable (n=54)	Gene-based (n=56)	Cell-replacement (n=44)
HbA1c change (%)	−1.2 ± 0.8	−0.6 ± 0.7	−0.8	−1.0
Insulin dose change (U/kg/day)	−0.18 ± 0.11	−0.08 ± 0.10	−0.10	−0.15
HbA1c <7% at endpoint, n (%)	14 (30%)	8 (14%)	13 (23%)	9 (20%)
≥50% insulin reduction, n (%)	18 (39%)	10 (19%)	13 (24%)	15 (34%)
Severe hypoglycemia during follow-up, n (%)	6 (13%)	12 (22%)	10 (18%)	—

Discussion

Over 6-months, HbA1c decreased by 0.9%, fasting glucose fell, and insulin dose declined, indicating clinically meaningful improvement in glycemic control. Three findings are notable. First, clinically meaningful improvement in glycemic control was observed over 6 months, with a 0.9% absolute reduction in HbA1c accompanied by lower fasting glucose and reduced insulin dose. Second, residual β-cell function appeared to modify response: participants with detectable C-peptide experienced larger HbA1c and insulin-dose reductions and a higher proportion achieving HbA1c <7%. Third, inflammatory activation was common at baseline, with more than one quarter meeting criteria for a high inflammatory state.

The magnitude and direction of metabolic change align with the concept that partial restoration of endogenous insulin secretion improves glycemic stability while reducing exogenous insulin requirements. DCCT analyses have shown that preserved C-peptide is associated with better glycemic profiles, fewer severe hypoglycemia events, and improved complication risk trajectories [2–4]. The present stratified results are consistent with this framework and support measuring C-peptide when evaluating response to emerging therapies. In addition, workshop guidance has emphasized the interpretive value of standardized C-peptide reporting, particularly when comparing heterogeneous interventions across studies [5].

Cell-based replacement approaches, including islet transplantation, have demonstrated benefits in selected patients with brittle diabetes and severe hypoglycemia. Classic reports of glucocorticoid-free islet transplantation and subsequent multicentre trials documented improved glycemic control and protection from severe hypoglycemia, even when insulin independence was not durable [7,8]. The small proportion achieving insulin independence in the current cohort, together with broader improvement in HbA1c and insulin dose, resembles transplantation patterns where graft function improves glycemic control and hypoglycemia risk even without durable insulin-free status [8,9]. Reviews of β-cell replacement strategies emphasize ongoing barriers related to immune rejection, access to scalable cell sources, and the need for safer immunomodulation [10,11].

Baseline inflammation could influence engraftment, immune tolerance, and metabolic response. IL-6 has been linked to higher inflammatory burden and suboptimal glycemic control in type 1 diabetes cohorts, supporting the rationale for monitoring this axis during advanced interventions [12]. Intensive glycemic control itself can modify inflammatory pathways, underscoring bidirectional relationships between glucose exposure and systemic inflammation [13]. In the CGM subset, the observed increase in time-in-range complements HbA1c change and reflects improved day-to-day glucose exposure; use of standardized CGM targets and wear-time criteria is supported by international consensus recommendations [6].

Taken together, these findings support integrated interpretation of metabolic endpoints with residual C-peptide and immune-inflammatory context. Gene-based interventions are being explored to enhance insulin production and immune regulation, but translation remains constrained by durability and safety considerations, as summarized in recent overviews [14]. Future work with longer follow-up, more granular intervention characterization, and longitudinal biomarker profiling would help clarify which patients derive sustained benefit and how immune modulation can be optimized alongside metabolic targets.

Limitations

This study has limitations. The single-centre observational design limits causal inference and generalizability. Intervention allocation followed clinical protocols rather than randomization, and the gene-based and cell-replacement categories represent heterogeneous approaches with variable dosing and immunosuppression. Follow-up was limited to 6 months, restricting assessment of durability and safety. CGM-derived time-in-range was available only in a subset, and some subgroup outcomes had incomplete documentation.

Conclusion

In this 6-month observational cohort of 100 individuals with type 1 diabetes receiving gene-based or cell-replacement interventions, HbA1c, fasting glucose, and insulin requirements all decreased. Nearly half achieved an HbA1c reduction of at least 1%, and a small subset attained insulin independence at endpoint. Residual C-peptide emerged as a pragmatic stratifier, with measurable C-peptide associated with larger improvements in HbA1c and insulin dose and fewer severe hypoglycemia events. Baseline inflammatory activation was frequent, reinforcing the value of parallel immune and metabolic monitoring. Longer prospective studies should evaluate durability, safety, and biomarker-guided patient selection using standardized CGM targets where available.

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