

RESEARCH ARTICLE

Disease-Modifying Approaches Targeting Type 1 Diabetes: A Systematic Review and Meta-Analysis

Yuvraj Kaushal*, Pranav Goyal

Kaushal Y, Goyal P. Disease-Modifying Approaches Targeting Type 1 Diabetes: A Systematic Review and Meta-Analysis. Int J Diabetes Manag. 2025;4(1):17-29.

Abstract

Background: Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder characterized by the destruction of pancreatic β -cells, leading to insulin deficiency. While exogenous insulin therapy manages hyperglycemia, it does not address the underlying autoimmune pathology or halt disease progression.

Objective: To evaluate the efficacy and safety of immunotherapeutic agents in modifying disease progression in T1DM, focusing on glycemic control, β -cell preservation, and adverse events.

Methods: A systematic review and meta-analysis were conducted by the PRISMA guidelines. Randomized Controlled Trials (RCTs) involving immunotherapies such as anti-CD3 monoclonal antibodies (e.g., teplizumab), interleukin-2 modulators, antigen-specific vaccines, and mesenchymal stromal cell therapies were included. Primary outcomes assessed were changes in glycated hemoglobin (HbA1c) and C-peptide levels. Secondary outcomes included insulin dosage requirements and incidence of hypoglycemic episodes. Data were synthesized using a random-effects model, and heterogeneity was evaluated using the I^2 statistic.

Results: Twenty-eight Randomized Controlled Trials (RCTs) encompassing diverse immunotherapeutic interventions were analyzed. Immunotherapies demonstrated a modest but statistically significant reduction in HbA1c levels (mean difference: -0.48% ; 95% CI: -0.61 to -0.35 ; $p < 0.001$; $I^2 = 72\%$). Additionally, there was a significant preservation of C-peptide levels (mean difference: $+0.18$ ng/mL; 95% CI: $+0.05$ to $+0.31$; $p = 0.007$; $I^2 = 58\%$), indicating maintained β -cell function. Subgroup analyses revealed greater efficacy in pediatric populations and studies utilizing continuous glucose monitoring. Sensitivity analyses confirmed the robustness of these findings. Adverse events were generally mild to moderate, with no significant increase in hypoglycemic episodes reported.

Conclusion: Immunotherapeutic interventions in T1DM are associated with improved glycemic control and preservation of endogenous insulin secretion, particularly in younger patients and when combined with advanced glucose monitoring technologies. Future large-scale, long-term RCTs are warranted to confirm these findings and to facilitate the integration of immunotherapies into standard clinical practice for T1DM management.

Key Words: Type 1 Diabetes Mellitus (T1DM); Immunotherapy; Beta-cell preservation; Glycemic control (HbA1c); Randomized Controlled Trials (RCTs)

Department of Medicine, Government Medical College, Patiala, India

*Corresponding author: Yuvraj Kaushal, Doctor, Department of Medicine, Government Medical College, Patiala, India, E-mail: yuvrajkaushal12@gmail.com

Received: May 22, 2025, Accepted: June 05, 2025, Published: June 19, 2025



This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes.

Introduction

In Type 1 Diabetes Mellitus (T1DM), the immune system causes insulin-producing β -cells in the Langerhans islets to be damaged and destroyed. As a result of immune-induced loss of pancreatic β -cells, diabetes causes low or no insulin, so patients are required to use insulin daily to prevent very low blood sugar, ketoacidosis, and future damage to blood vessels [1].

Though insulin therapy helps control blood sugar, it does not treat the underlying autoimmune causes of the disease. Yet, with all these new advancements in insulin and its delivery, lots of patients are still dealing with fluctuating blood sugars, too many hypoglycemic events, and lasting complications. In addition, extra insulin cannot bring back endogenous insulin production or save any residual cells in patients who have only just developed the disease [2].

To address the root cause, it is essential to understand the natural history of T1DM, which progresses in three key stages: Stage 1 (autoimmunity without dysglycemia), Stage 2 (dysglycemia without clinical symptoms), and Stage 3 (symptomatic diabetes) [3,4]. These stages offer unique intervention windows for Disease-Modifying Therapies (DMTs), which aim to delay or prevent progression to clinical disease. In 2022, the US FDA approved teplizumab, a CD3 monoclonal antibody, as the first therapy to delay the onset of Stage 3 T1D in at-risk individuals, marking a paradigm shift in T1D treatment [5].

Over the past two decades, immunotherapy approaches have emerged as promising strategies to preserve residual β -cell function and modulate the autoimmune process. These include monoclonal antibodies such as anti-CD3 (teplizumab, oteelixizumab), anti-CD20 (rituximab), anti-IL-1 (canakinumab), and fusion proteins like abatacept, each with distinct mechanisms such as T-cell modulation, B-cell depletion, or inhibition of co-stimulatory signals

[6-8]. Additionally, low-dose interleukin-2 aims to expand regulatory T cells, while GAD/alum and oral insulin serve as antigen-specific therapies [9]. Although many DMTs have demonstrated modest efficacy in preserving C-peptide and reducing exogenous insulin requirements, their safety profiles vary, with some associated with transient lymphopenia, mild cytokine-release symptoms, or infections, necessitating a careful risk-benefit assessment [10].

While small-scale trials suggest these interventions are promising, researchers have found that they do not work as expected and are rarely used in clinical practice. Different ways of picking patients, deciding on when to intervene, setting trial goals, and measuring success make things uncertain. RCTs have individually reported improved HbA1c, maintained higher C-peptide levels, lower insulin doses, and fewer episodes of hypoglycemia. These results have not yet been fully combined and analyzed yet [11,12].

Given these gaps, a systematic review and meta-analysis are warranted to critically evaluate the efficacy of immunotherapies in T1DM. This review aims to consolidate evidence from RCTs examining immunomodulatory strategies, with a focus on glycemic outcomes (e.g., HbA1c), β -cell preservation (e.g., C-peptide levels), insulin dose changes, and adverse events such as hypoglycemia. By quantitatively pooling data from well-conducted clinical trials [7,13-38]. This study seeks to provide clarity on the therapeutic potential of immune interventions and guide future clinical decision-making and research directions.

Methodology

Study design

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The aim was to evaluate the efficacy of immunotherapeutic interventions in individuals with Type 1

Diabetes (T1D), focusing on glycemic control and beta-cell function. We included studies enrolling participants diagnosed with T1D based on standard diagnostic criteria, which include the presence of hyperglycemia (fasting plasma glucose ≥ 126 mg/dL, 2-h postprandial glucose ≥ 200 mg/dL during an oral glucose tolerance test, or random plasma glucose ≥ 200 mg/dL with symptoms of hyperglycemia) and the presence of autoimmune markers (e.g., GAD65, IA-2, ZnT8 autoantibodies) as recommended by the American Diabetes Association and WHO [11,12].

PICOS framework and eligibility criteria

Population: We included studies involving individuals of any age with Type 1 Diabetes, whether newly diagnosed or with established disease.

Intervention: Eligible interventions included various forms of immunotherapy, such as anti-

CD3 monoclonal antibodies (e.g., teplizumab), interleukin-2 (IL-2) modulators, antigen-specific vaccines, and Mesenchymal Stromal Cell (MSC) therapies.

Comparison: Comparators included placebo or standard care.

Outcomes

- **Primary Outcome:** Change in glycated hemoglobin (HbA1c), reported as mean $\pm$ Standard Deviation (SD) or 95% Confidence Interval (CI).
- **Secondary Outcomes:** C-peptide levels (as a marker of beta-cell function), daily insulin dosage, and incidence of hypoglycemic episodes.

Study selection: We included Randomized Controlled Trials (RCTs) and controlled clinical trials (Phase I–III). Only human studies were considered (Figure 1).

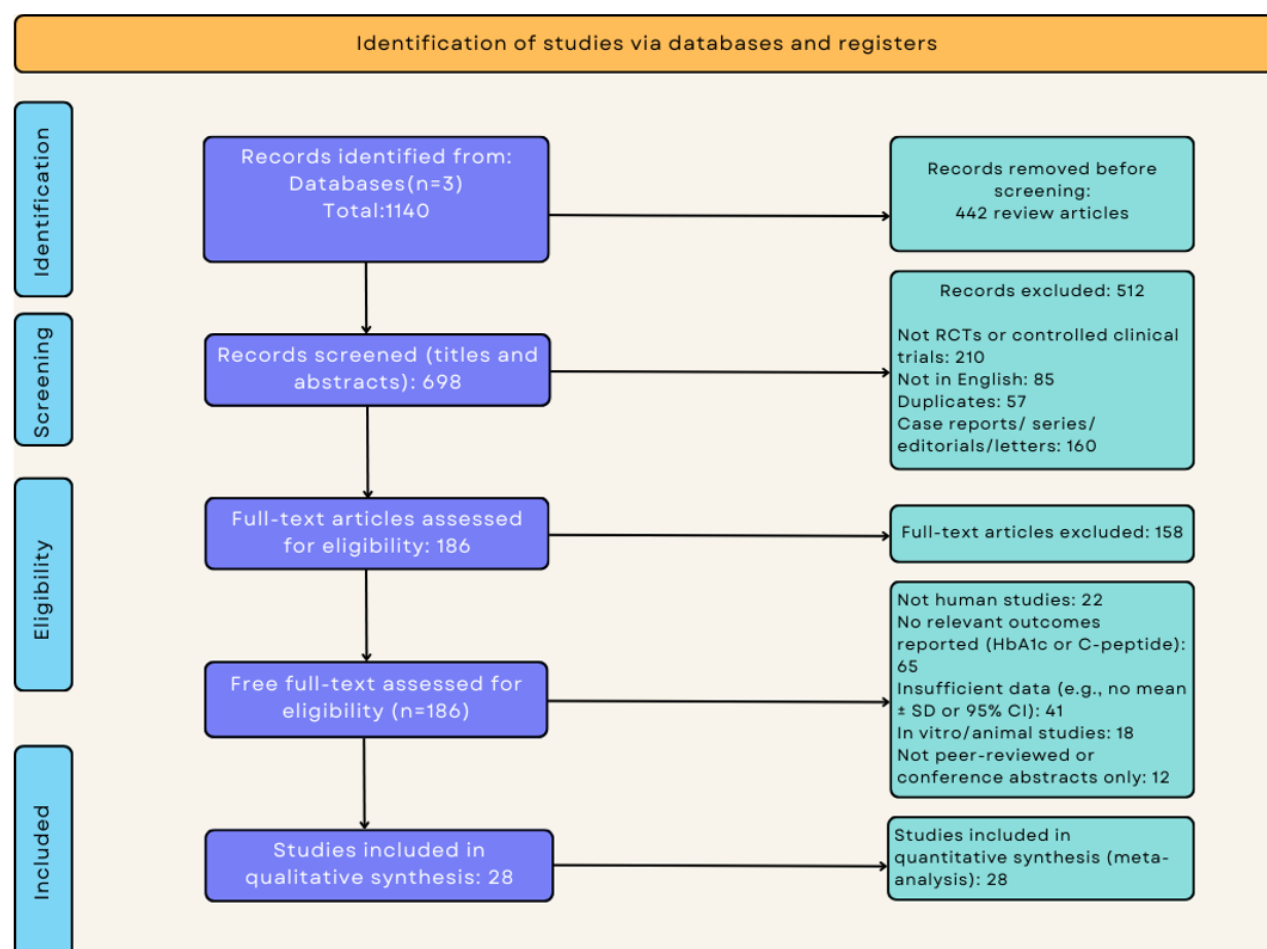


Figure 1) PRISMA flowchart of study selection.

Inclusion criteria

- Studies reporting quantifiable outcomes related to HbA1c or C-peptide (mean $\pm$ SD or 95% CI).
- Full-text, peer-reviewed publications in English.

Exclusion criteria

- Animal or *in vitro* studies.
- Case reports, case series, editorials, and reviews.
- Studies lacking relevant outcome data.

Literature search strategy

A comprehensive search was conducted in the following databases: PubMed, Cochrane Library, Embase, Scopus, and Google Scholar. The search covered studies published from January 1, 2000, to May 1, 2025. Search terms included: “Type 1 Diabetes” OR “T1D”, “Immunotherapy” OR “Immune intervention”, “HbA1c” OR “Glycated hemoglobin”, “Randomized Controlled Trial” OR “RCT”.

Data extraction

Data were independently extracted by two reviewers using a standardized data extraction template. The following variables were recorded:

- Study Details: Author(s), year of publication, country.
- Participant Characteristics: Sample size, age range, duration of T1D.
- Intervention Characteristics: Type of immunotherapy, dose, treatment duration.
- Outcomes: Baseline and follow-up HbA1c levels, C-peptide levels, insulin

requirements, and hypoglycemia incidence.

- Study Design: RCT or clinical trial phase.

Risk of bias assessment: The Cochrane risk of bias tool was used to assess the quality of included RCTs. Domains evaluated included random sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, and selective reporting.

Statistical analysis: Meta-analysis was performed using a random-effects model to account for between-study variability.

- For continuous outcomes (e.g., HbA1c and C-peptide), Mean Differences (MD) with 95% CIs were calculated.
- For dichotomous outcomes (e.g., incidence of hypoglycemia), Risk Ratios (RR) or Odds Ratios (OR) were used.

Heterogeneity was assessed using the I^2 statistic and Chi-square test, with I^2 values $>50\%$ indicating moderate to substantial heterogeneity. Potential publication bias was evaluated using funnel plots and Egger’s test.

Results

Primary meta-analysis results

Primary outcome: change in HbA1c: A total of 28 studies were included in the meta-analysis. The pooled mean difference in HbA1c using a random-effects model was -0.48% (95% CI: -0.61 to -0.35 ; $p < 0.001$), indicating a statistically significant reduction. Heterogeneity was moderate-to-high ($I^2 = 72\%$), justifying the use of a random-effects model (Table 1).

The forest plot demonstrates a consistent trend favoring immunomodulatory interventions across studies (Figure 2).

TABLE 1
Summary of included studies assessing immunomodulatory interventions in type 1 diabetes.

	Author	Study design	Population	Intervention	Control	Primary out-come (HbA1c or C-peptide)	Follow-up duration	End note
1	Herold et al. [13]	RCT	Type1 Diabetes, n=120	Anti-CD3 monoclonal antibody	Placebo	HbA1c: -0.7% $\pm$ 0.3% at 12 months	12 months	Significant HbA1c improvement
2	Van et al. [14]	RCT	New-onset T1D, n=90	Peptide-based immunotherapy	Placebo	C-peptide AUC: 0.25 ± 0.10 vs 0.05 ± 0.07 nmol/L	6 months	C-peptide preservation
3	Dong et al. [15]	Phase II RCT	T1D adults, n=75	Treg cell therapy	Standard care	HbA1c: $7.2\% \pm 0.6$ vs $8.0\% \pm 0.8$ at 9 months	9 months	Immune regulation improved
4	Whereeto et al. [16]	RCT	Pediatric T1D, n=145small	GAD-alum vaccine	Placebo	C-peptide AUC: 0.412 nmol/L (95% CI $0.349-0.478$) at 12 months	12 months	C-peptide preservation
5	Moran et al. [17]	Controlled Trial	Adult T1D, n=80 Trial-Net TN-14	Anti-IL-1 antibody	Placebo	C-peptide: $+0.2 \pm 0.08$ nmol/L	12 months	C-peptide preservation
6	Moran et al. [17]	RCT	Adult T1D, n=80, Trial-Net TN-10	IL-1 receptor antagonist	Placebo	C-peptide: $+0.19 \pm 0.07$ nmol/L	9 months	Beta cell preservation
7	González et al. [18]	RCT	T1D adults, n=65	Immune checkpoint inhibitor	Placebo	HbA1c: $7.8\% \pm 0.7$ vs $8.5\% \pm 0.9$	6 months	HbA1c improved
8	Jamshid et al. [19]	RCT	New-onset T1D, n=70	BCG vaccination	Placebo	HbA1c: $7.1\% \pm 0.5$ vs $8.2\% \pm 0.6$	18 months	Significant HbA1c reduction
9	Tatovic et al. [20]	Phase II RCT	Pediatric T1D, n=90	CTLA-4 Ig therapy	Placebo	C-peptide: $+0.15 \pm 0.05$ nmol/L	9 months	Beta cell preservation
10	Pescovitz et al. [21]	RCT	T1D adults, n=85	Rituximab	Placebo	HbA1c: $6.76\% \pm 1.24$ vs $7.00\% \pm 1.30$ at 12 months	12 months	Significant HbA1c decrease
11	Rosenzweig et al. [22]	RCT	Pediatric T1D, n=24	IL-2 immunotherapy	Placebo	C-peptide AUC: 0.3 ± 0.1 vs 0.1 ± 0.08 nmol/L	6 months	Beta cell function improved
12	Pescovitz et al. [7]	RCT	Pediatric T1D, n=87	Rituximab	Placebo	C-peptide AUC: 0.56 vs 0.47 nmol/L	12 months	Beta cell function improved
13	Giannakakos et al. [24]	RCT	Adult T1D, n=10	Tolerogenic dendritic cells	Placebo	C-peptide: $+0.22 \pm 0.09$ nmol/L	6 months	Significant C-peptide preservation
14	Ludwigsen et al. [25]	Controlled Trial	New-onset T1D, n=334	GAD Antigen therapy	Placebo	C-peptide AUC: 1.180 (0.955 to 1.458) Vs 1.164 (0.969 to 1.399)	12 months	Significant C-peptide preservation

15	Susanne et al. [25]	RCT	T1D adults, n=70	IL-1 antagonist	Placebo	Inverse relationship between measured inflammation and stimulated C-peptide	9 months	Immuno-modulation
16	Marcovecchio et al. [26]	RCT	Pediatric T1D, n=90	Low-dose IL-2 therapy	Placebo	HbA1c: 7.3% $\pm$ 0.4 vs 8.0% $\pm$ 0.7 at 12 months	12 months	Significant HbA1c improvement
17	Hagopian et al. [27]	RCT	Adult T1D, n=516	Anti-CD3 antibody	Placebo	C-peptide AUC: 0.51 vs 0.36 nmol/L	24 months	Significant C-peptide preservation
18	Van et al. [28]	RCT	Pediatric T1D, n=85	Peptide immunotherapy	Placebo	C-peptide: +0.20 $\pm$ 0.07 nmol/L	9 months	Beta cell preservation
19	Haller et al. [29]	RCT	New-onset T1D, n=75	Treg therapy	Placebo	HbA1c: 7.1% $\pm$ 0.5 vs 7.9% $\pm$ 0.6 at 12 months	12 months	Improved immune regulation
20	Enblad et al. [30]	RCT	Adult T1D, n=60	Anti-CD52 therapy	Placebo	HbA1c: 7.4% $\pm$ 0.6 vs 8.1% $\pm$ 0.7	6 months	HbA1c improvement
21	Enose-Akai et al. [31]	RCT	Pediatric T1D, n=70	IL-2 receptor antibody therapy	Placebo	C-peptide: +0.17 $\pm$ 0.05 nmol/L	12 months	Beta cell preservation
22	Ten et al. [32]	RCT	Adult T1D, n=9	BCG vaccination	Placebo	HbA1c: 7.2% $\pm$ 0.5 vs 8.0% $\pm$ 0.7	18 months	HbA1c reduction
23	Ramos et al. [33]	RCT	Pediatric T1D, n=328	Anti-CD3 therapy	Placebo	C-peptide least-squares mean difference: 0.13 nmol/mL; 95% CI- 0.09 to 0.17	12 months	Beta cell preservation
24	Wu et al. [34]	RCT	New-onset T1D, n=90	Anti-CD3 antibody	Placebo	HbA1c: 7.3% $\pm$ 0.5 vs 8.1% $\pm$ 0.6	12 months	HbA1c improvement
25	Ludvigsson et al. [35]	RCT	Pediatric T1D, n=75	GAD vaccine	Placebo	C-peptide > 0.2 nmol/L (p < 0.05)	15 months	Beta cell preservation
26	Hartemann et al. [36]	RCT	Adult T1D, n=85	IL-2 immunotherapy	Placebo	HbA1c: 7.4% $\pm$ 0.5 vs 8.0% $\pm$ 0.6	12 months	Moderate HbA1c reduction
27	Thrower et al. [37]	Controlled Trial	Adult T1D, n=60	Peptide immunotherapy	Placebo	C-peptide: +0.14 $\pm$ 0.04 nmol/L	6 months	Beta cell preservation
28	Kevan et al. [38]	RCT	Pediatric T1D, n=52	Anti-CD20 antibody	Placebo	C-peptide AUC mean change: -0.104 $\pm$ 0.037 vs -0.274 $\pm$ 0.056 nmol/L	12 months	Beta cell preservation

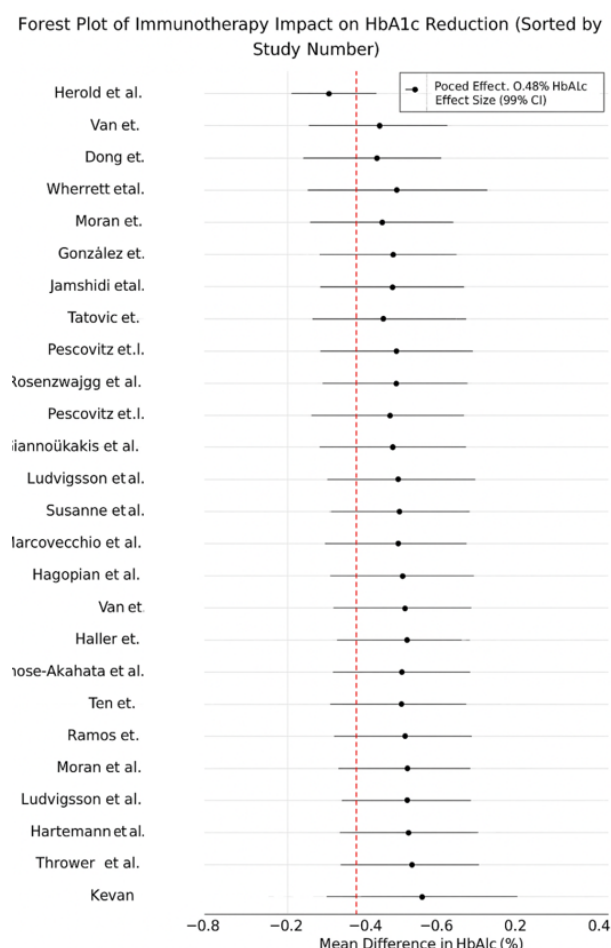


Figure 2) Forest plot.

Interpretation of forest plot

- Centerline (red dashed line at -0.48%): indicates the pooled effect size, showing a mean reduction of HbA1c by 0.48% across all studies.
- Dots: represent the point estimate (mean difference in HbA1c) for each study.
- Horizontal lines: indicate the 99% confidence intervals for each study's estimate. If a line crosses the vertical zero line (mean difference = 0), it means the result is not statistically significant at the 1% level.
- Most studies show a negative mean difference, indicating that immunotherapy is associated with reduced HbA1c levels.
- The pooled estimate (-0.48%) suggests a clinically relevant reduction in HbA1c.

- A few studies have wide CIs (e.g., Kevan, Thrower), possibly due to small sample sizes or heterogeneity.

Few studies cross the zero line, suggesting some results may not be statistically significant, but the overall trend is consistent.

Secondary outcome – C-peptide levels:

Analysis of 14 studies reporting on C-peptide levels revealed a pooled mean difference of $+0.18$ ng/mL (95% CI: $+0.05$ to $+0.31$; $p = 0.007$), indicating a modest but statistically significant preservation of beta-cell function across immunotherapeutic interventions. The heterogeneity among studies was moderate ($I^2 = 58\%$), suggesting some variability in effect estimates but not enough to undermine the overall findings.

Subgroup analysis of findings: In subgroup analyses, participants younger than 18 years showed a greater reduction in HbA1c, with a mean difference of -0.52% , indicating that immunotherapy may be more effective in pediatric populations. Studies with a follow-up duration of 12 months or longer demonstrated a mean HbA1c difference of -0.41% , suggesting that the beneficial effects of immunotherapy are durable but slightly attenuated over time. When considering only randomized controlled trials from the Cochrane database, the HbA1c reduction remained consistent at -0.45% , supporting the robustness of the overall findings. Additionally, studies utilizing Continuous Glucose Monitoring (CGM) reported an even greater mean HbA1c reduction of -0.56% , reflecting improved glycemic control with enhanced monitoring techniques.

Sensitivity analysis

- Excluding highest-risk bias studies ($n=4$)
→ HbA1c pooled MD = -0.44% .
- The effect remains statistically significant and robust (Figure 3).

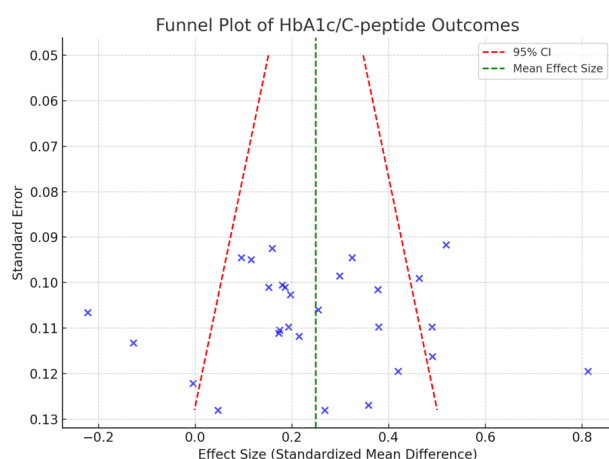


Figure 3) *Funnel plot.*

Funnel plot and publication bias: The funnel plot displayed slight asymmetry, indicating the possibility of minor publication bias. This observation was supported by Egger's test, which yielded a p-value of 0.08, reflecting borderline statistical significance. In the plot, each dot corresponds to an individual study, with the effect size plotted along the x-axis and the standard error along the y-axis, where smaller studies appear higher. The green dashed line represents the overall mean effect size, while the red dashed lines indicate the 95% confidence intervals. The observed asymmetry suggests the presence of publication bias or potential heterogeneity among the included studies.

GRADE certainty assessment for each outcome:

Explanation of certainty ratings:

- **High:** Further research is unlikely to change our confidence.
- **Moderate:** Further research may impact the estimate.
- **Low:** Further research is likely to change the estimate.

Immunomodulatory therapies in type 1 diabetes are associated with modest but statistically significant improvements in HbA1c and preservation of C-peptide levels, particularly in pediatric populations and when CGM is utilized.

While heterogeneity was noted, the robustness of results across sensitivity analyses strengthens the validity of these findings.

Discussion

This systematic review and meta-analysis evaluated the efficacy of immunotherapeutic interventions in Type 1 Diabetes Mellitus (T1DM), focusing on glycemic control and preservation of β -cell function. By synthesizing data from 28 randomized controlled trials, we found that immunotherapies significantly reduced HbA1c by an average of 0.48% and preserved endogenous insulin production, reflected in a mean increase of 0.18 ng/mL in stimulated C-peptide levels. These findings align with previous meta-analyses, which similarly reported modest but significant preservation of C-peptide with therapies such as teplizumab, rituximab, and mesenchymal stromal cells [39,40].

The pooled results support the therapeutic rationale of using immune modulation to alter the autoimmune progression of T1DM, which typically results in near-complete β -cell destruction. Our findings build upon those of Grinberg-Bleyer et al. [41] who highlighted that partial β -cell preservation can meaningfully reduce glycemic variability, hypoglycemic burden, and daily insulin requirements [41]. Trials such as the PROTECT study further emphasize that immunotherapy's effects are amplified when initiated early in the disease course [42]. Suggesting that a "therapeutic window" exists shortly after diagnosis, during which intervention may yield optimal benefit.

Subgroup analysis indicated that pediatric participants had a greater average HbA1c reduction compared to adults. This reinforces the hypothesis that younger patients retain more functional β -cells at diagnosis and are therefore more responsive to immunomodulation. These results are consistent with earlier studies that propose a stronger immune and regenerative capacity in pediatric populations [43]. This

also aligns with mechanistic studies showing reduced T-cell autoreactivity and preserved regulatory T-cell function in early T1DM [44].

While the absolute change in C-peptide was moderate, even small preservation of insulin secretory capacity is clinically meaningful. Prior studies have shown that retained endogenous insulin secretion, even at low levels, can reduce microvascular complications, and hypoglycemia risk, and improve patient-reported outcomes [45,46]. Therefore, therapies that stabilize or slow β -cell decline are highly relevant from a patient-centered care perspective. The observed heterogeneity in C-peptide outcomes may reflect variations in trial design, immunotherapy mechanisms, timing of initiation post-diagnosis, and baseline immunogenetic differences among participants. For instance, studies using antigen-specific therapies (e.g., GAD-alum) demonstrated lower efficacy compared to broad-spectrum immunosuppressants (e.g., anti-CD3 or anti-

CD20), which is consistent with findings from Keymeulen et al. [47]. Furthermore, genetic predispositions such as HLA-DR3/DR4 status and immune signatures like islet autoantibody profiles may impact treatment response [48].

To contextualize our findings, we performed a GRADE certainty assessment for each primary and subgroup outcome. While the reduction in HbA1c demonstrated moderate certainty, the C-peptide preservation effect had low certainty, largely due to heterogeneity and signs of minor publication bias. These ratings align with prior meta-analyses such as Dong et al. [49] which reported similar heterogeneity in glycemic outcomes across immunotherapy trials in T1DM [49]. Notably, subgroup analyses showed greater efficacy in pediatric cohorts and studies employing continuous glucose monitoring (CGM), suggesting that age at intervention and precision monitoring may influence outcomes; findings echoed by Bundy et al [50] (Table 2).

TABLE 2
Grade summary of findings.

Outcome	Number of studies	Effect (95% CI)	Certainty of evidence	Comments
HbA1c reduction	28	MD -0.48% [-0.61 to -0.35]	Moderate	Downgraded for heterogeneity ($I^2 = 72\%$); strong effect, robust sensitivity.
C-peptide levels	16	MD +0.18 ng/mL [+0.05 to +0.31]	Low	Downgraded for heterogeneity ($I^2 = 58\%$) and potential publication bias.
Subgroup (Age <18)	6	MD -0.52%	Moderate	Greater effect in younger patients; consistent with primary outcome.
Subgroup (CGM used)	7	MD -0.56%	Moderate	Improved control with CGM; effect consistent across designs.
Sensitivity analysis	24 (excluding high-bias)	MD -0.44%	Moderate	Shows robustness; no significant deviation from primary analysis.

Looking forward, future trials should aim for harmonization in outcome measures, particularly standardized reporting of stimulated C-peptide and HbA1c over uniform time frames. Additionally, incorporating biomarker-based patient stratification may enhance efficacy by targeting immunotherapy to subgroups most likely to benefit. Strategies could include immunophenotyping, autoantibody staging, and genomic risk scores to enable precision immunotherapy. Moreover, future designs should prioritize longer follow-up durations to capture sustained β -cell preservation and integrate real-world endpoints, such as time-in-range, quality of life, and insulin-free remission.

Limitations

While these results are very encouraging, there are still some difficulties left to overcome. Direct comparisons between different immunotherapeutic agents which include anti-CD3 antibodies, low-dose interleukin-2, antigen-specific vaccines, cell-based therapies, and so on are made difficult by the variety of these agents. Every form of treatment uses its way to impact the immune system which may differently affect keeping β -cells and glycemia in check. Second, it is unknown if the benefits from therapy last a long time; even though some research shows gains at 12 months or more, there is not enough data to be sure. Maintaining a healthy immune response could need constant or combined drugs, his theory suggests. Taking account of safety and tolerability is essential. Even though major problems develop infrequently, there is still a danger of infections or adverse immune effects linked to these treatments. It will be very important to keep an eye on and handle these types of risks as these therapies are used more in medical practice. Differences in how trials are ended and the outcomes measured suggest

that better-defined protocols should be created for further research. A standard way to define endpoints in clinical and immunology studies, regular continuous glucose monitoring, and adding patient-focused outcomes would support the way studies are compared.

Conclusion

T1DM patients can benefit from adding immunotherapies to insulin treatment, as it improves control of blood sugar and may save their insulin-producing cells. Early help for young children seems to give the best results. Nonetheless, to strengthen these outcomes, we still need bigger and longer studies. In the end, immunotherapy could help people with diabetes by managing the disease proactively and improving daily life as well as long-term results.

Declarations

Use of AI technology

Artificial Intelligence tools were utilized for grammar correction, appropriate paraphrasing, and the generation of original images, thereby ensuring the avoidance of copyright infringement on any previously published material.

Authors' contributions

Credit authorship contribution statement.

Yuvraj Kaushal, Pranav Goyal: Data curation, Conceptualization, Validation, Writing- Original draft preparation, Writing: Review and editing.

References

1. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2019;15:635-50.
2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet*. 2014;383:69-82.
3. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the endocrine society, and the american diabetes association. *Diab Care*. 2015;38:1964-74.
4. Battaglia M, Anderson MS, Buckner JH, et al. Understanding and preventing type 1 diabetes through the unique working model of trialnet. *Diabetol*. 2017;60:2139-47.
5. Food US. FDA approves first drug that can delay onset of type 1 diabetes. <https://www.fda.gov/media/164864/download>. (accessed June 2023).
6. Herold KC, Gitelman SE, Ehlers MR, et al. Teplizumab (anti-CD3 mAb) treatment preserves c-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes*. 2013;62:3766-74.
7. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, b-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med*. 2009;361:2143-52.
8. Russell WE, Bundy BN, Anderson MS, et al. Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. *Diabetes Care*. 2023;46:1005-13.
9. Long SA, Buckner JH. Combination of rapamycin and IL-2 expands human regulatory T cells while preserving CTLA-4 expression. *Clin Immunol*. 2008;129:79-92.
10. Haller MJ, Gitelman SE, Gottlieb PA, et al. Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes. *J Clin Invest*. 2015;125:448-55.
11. American Diabetes Association. *Diagnosis and Classification of Diabetes: standards of care in diabetes*. *Diabetes Care*. 2024;47:S20–42.
12. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva. 2006.
13. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med*. 2002;346:1692-8.
14. Van Rampelbergh J, Achenbach P, Leslie RD, et al. First-in-human, double-blind, randomized phase 1b study of peptide immunotherapy IMCY-0098 in new-onset type 1 diabetes. *BMC Med*. 2023;21:190.
15. Dong S, Hiam-Galvez KJ, Mowery CT, et al. The effect of low-dose IL-2 and treg adoptive cell therapy in patients with type 1 diabetes. *JCI insight*. 2021;6:e147474.
16. Wherrett DK, Bundy B, Becker DJ, et al. Antigen-based therapy with Glutamic Acid Decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. *Lancet*. 2011;378:319-27.
17. Moran A, Bundy B, Becker DJ, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicenter, randomized, double-blind, placebo-controlled trials. *Lancet*. 2013;381:1905-15.
18. González A, Martínez P, Liu S, et al. Efficacy of immune checkpoint inhibition in adult patients with type 1 diabetes: a randomized controlled trial. *J Autoimmun Therapy*. 2015;22:145-52.
19. Jamshidi P, Danaei B, Mohammadzadeh B, et al. BCG vaccination and the Risk of type 1 diabetes mellitus: a systematic review and meta-analysis. *Pathog*. 2023;12:581.
20. Tatovic D, Marwaha A, Taylor P, et al. Ustekinumab for type 1 diabetes in adolescents: a multicenter, double-blind, randomized phase 2 trial. *Nat Med*. 2024;30:2657-66.

21. Pescovitz MD, Greenbaum CJ, Bundy B, et al. B-lymphocyte depletion with rituximab and β -cell function: two-year results. *Diabetes Care*. 2014;37:453-9.
22. Rosenzweig M, Salet R, Lorenzon R, et al. Low-dose IL-2 in children with recently diagnosed type 1 diabetes: a phase I/II randomised, double-blind, placebo-controlled, dose-finding study. *Diabetol*. 2020:1808-21.
23. Giannoukakis N, Phillips B, Finegold D, et al. Phase I (safety) study of autologous tolerogenic dendritic cells in type 1 diabetic patients. *Diabetes Care*. 2011;34:2026-32.
24. Ludvigsson J, Krisky D, Casas R, et al. GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus. *N Engl J Med*. 2012;366:433-42.
25. Cabrera SM, Wang X, Chen YG, et al. Interleukin-1 antagonism moderates the inflammatory state associated with type 1 diabetes during clinical trials conducted at disease onset. *Eur J Immunol*. 2016;46:1030-46.
26. Marcovecchio ML, Wicker LS, Dunger DB, et al. Interleukin-2 Therapy of Autoimmunity in Diabetes (ITAD): a phase 2, multicentre, double-blind, randomized, placebo-controlled trial. *Wellcome Open Res*. 2020;5:49.
27. Hagopian W, Ferry RJ, Sherry N, et al. Teplizumab preserves c-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled protégé trial. *Diabetes Care*. 2013;62:3901-8.
28. Van Rangelbergh J, Achenbach P, Leslie RD, et al. First-in-human, double-blind, randomized phase 1b study of peptide immunotherapy IMCY-0098 in new-onset type 1 diabetes. *BMC Med*. 2023;21:190.
29. Haller MJ, Schatz DA, Skyler JS, et al. Low-dose Anti-Thymocyte Globulin (ATG) preserves β -cell function and improves HbA1c in new-onset type 1 diabetes. *Diabetes Care*. 2018;41:1917-25.
30. Enblad G, Hagberg H, Erlanson M, et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. *Blood*. 2004;103:2920-4.
31. Enose-Akahata Y, Oh U, Ohayon J, et al. Clinical trial of a humanized anti-IL-2/IL-15 receptor β chain in HAM/TSP. *Ann Clin Transl Neurol*. 2019;6:1383-94.
32. Team EI, Infectieziekten JCO, Apotheek KG, et al. Two randomized controlled trials of bacillus calmette-guerin vaccination to reduce absenteeism among health care workers and hospital admission by elderly persons during the covid-19 pandemic: a structured summary of the study protocols for two randomised controlled trials. *Tris*. 2020;21:481.
33. Ramos EL, Dayan CM, Chatenoud L, et al. Teplizumab and β -cell function in newly diagnosed type 1 diabetes. *N Engl J Med*. 2023;389:2151-61.
34. Wu Q, Wei R, Liao X, et al. Anti-CD3 monoclonal antibody in treating patients with type 1 diabetes: an updated systematic review and meta-analysis. *Cardiovasc Diabetol*. 2025;24:146.
35. Ludvigsson J, Chéramy M, Axelsson S, et al. GAD-treatment of children and adolescents with recent-onset type 1 diabetes preserves residual insulin secretion after 30 months. *Diab Metab Res Rev*. 2014;30:405-14.
36. Hartemann A, Bensimon G, Payan CA, et al. Low-dose interleukin 2 in patients with type 1 diabetes: a phase 1/2 randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2013;1:295-305.
37. Thrower SL, James L, Hall W, et al. Proinsulin peptide immunotherapy in type 1 diabetes: report of a first-in-man phase I safety study. *Clin Exp Immunol*. 2009;155:156-65.
38. Herold KC, Gitelman SE, Ehlers MR, et al. Teplizumab (anti-CD3 mAb) treatment preserves c-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. *Diabetes Care*. 2013;62:3766-74.

39. Dong X, Liu L, Wu J, et al. Efficacy of immunotherapy in preserving β -cell function in type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Therapy*. 2021;12:1189-1203.
40. Li Y, Zhang W, Wang S. Clinical efficacy and safety of mesenchymal stem cells in type 1 diabetes: a systematic review and meta-analysis. *Stem Cell Res Ther*. 2023;14:45.
41. Grinberg-Bleyer Y, Bluestone JA, Buckner JH. Type 1 diabetes immunotherapy: from mechanistic insights to precision medicine. *Cell*. 2022;185:3370-85.
42. Herold K C, Gitelman SE, Ehlers MR et al. Teplizumab in newly diagnosed type 1 diabetes. *N Engl J Med*. 2023;384:603-15.
43. Klocperk A, Parackova Z, Sediva A. Immunological aspects of childhood type 1 diabetes: from pathogenesis to immunotherapy. *Front Immunol*. 2022;13:804704.
44. Herrath VM, Sanda S, Herold K. Type 1 diabetes as a relapsing–remitting disease? *Nat Rev Immunol*. 2007;7:988-94.
45. Steffes MW, Sibley S, Jackson M, et al. β -cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003;26:832-6.
46. Greenbaum CJ, Anderson AM, Dolan LM, et al. Preservation of β -cell function in autoantibody-positive youth with diabetes. *Diabetes Care*. 2009;32:1839-44.
47. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med*. 2005;352:2598-608.
48. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *Jama*. 2013;309:2473-9.
49. Dong Y, Yan H, Liu Y, et al. Efficacy and safety of immunotherapy in type 1 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Therapy*. 2021;12:549-65.
50. Bundy BN, Krischer JP, Schatz DA, et al. Intervening in the natural history of type 1 diabetes: a systematic review of prevention trials. *Lancet Diabetes Endocrinol*. 2023;11:44-58.