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The Effectiveness of Stem Cell Therapy Compared to Conventional Therapy on Improving Pancreatic Beta Cell Function in Type 2 Diabetes Patients: A Systematic Review

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Abstract
More than 800 million people worldwide experience type 2 diabetes mellitus (T2DM), characterized by progressive pancreatic β-cell deterioration inadequately addressed by conventional treatments. This review assesses stem cell-based interventions versus standard therapy for β-cell functional restoration. Systematic review aims to comprehensively evaluate and compare the effectiveness of stem cell therapy versus conventional therapy in improving pancreatic β-cell function in type 2 diabetes patients. Systematic searches of PubMed, Cochrane Library, Web of Science, and Scopus from January 2015 to October 2025 retrieved 125 records. After duplicate removal and screening, 17 studies met the general inclusion criteria, of which six randomized controlled trials (RCTs) involving 339 participants were eligible for analysis. Primary outcomes were C-peptide concentrations, HOMA-β, HbA1c, insulin requirements, and safety parameters. The results showed that stem cell interventions consistently elevated fasting C-peptide levels to 1.9±1.0 ng/mL (versus 0.7±0.4 ng/mL in controls). Mean HbA1c reductions reached 0.67% (intervention 7.52±1.07% versus placebo 8.19±1.02%). Insulin dosage requirements decreased markedly, with reductions approaching 46.7%. Safety assessment remained limited due to incomplete adverse event documentation across included studies. Interpretation is further constrained by small trial sizes (23–91 participants) and protocol heterogeneity across cell sources, administration routes, and follow-up durations. Stem cell-based therapies demonstrate encouraging potential for enhancing pancreatic β-cell function in T2DM patients. Insufficient long-term follow-up data and inadequate safety surveillance preclude definitive clinical recommendations, supporting their application exclusively within structured clinical trial settings.

INTRODUCTION

The worldwide prevalence of type 2 diabetes mellitus has reached epidemic proportions, currently impacting more than 800 million people globally, with its defining features being the gradual deterioration of pancreatic β-cell function alongside resistance to insulin in peripheral tissues (Ogieuhi et al., 2025; Khin et al., 2023; Cerf, 2013; Almaça et al., 2020; Ukratalo et al., 2023; Pangemanan et al., 2023; Syuaib et al., 2025). A substantial depletion of β-cell mass—

approximately 40% to 60%—constitutes the pathophysiological cornerstone, further compounded by functional impairment driven by mechanisms including oxidative damage, pro-inflammatory cytokines, and cellular stress within the endoplasmic reticulum (Weir & Bonner-Weir, 2004; Eguchi et al., 2021; Serbis et al., 2023; Kaihena et al*.,* 2024).

Traditional pharmacotherapeutic interventions such as metformin, sulfonylureas, and exogenous insulin administration primarily focus on achieving glycemic regulation via enhanced insulin sensitivity or hormone supplementation, yet these approaches do not rectify the fundamental β-cell pathology (DeFronzo & Abdul-Ghani, 2011; Baker et al., 2021; Ukratalo et al*.* 2022; Kaihena et al*.,* 2023; Ukratalo et al., 2024; Kaihena et al*.,* 2024a; Petrie et al., 2024; Kalyani et al., 2025; Kakisina & Ukratalo, 2025). Although initially effective, these treatment modalities exhibit declining efficacy over extended periods, with roughly 50% of patients showing inadequate therapeutic response within three years and approximately 75% within nine years, requiring treatment intensification without reversing the underlying β-cell deterioration (Matthews et al., 2023). Novel regenerative approaches employing stem cell-derived therapies have emerged as potentially transformative interventions capable of addressing this critical therapeutic gap by promoting β-cell regeneration and restoring functional capacity (Shalaby & Abdelalim, 2020; Feng et al., 2024; Zang et al., 2017; Wu et al., 2024; Ghoneim et al., 2024).

Contemporary developments in stem cell research have revealed substantial therapeutic promise through diverse pathways encompassing transformation into insulin-secreting cells, modulation of immune responses, and β-cell preservation via paracrine signaling (Habiba et al., 2024; Bayat et al., 2024; Cho et al., 2018; Li et al., 2016; Aringazina et al., 2025). Mesenchymal stem cells obtained from different tissue origins have shown effectiveness in ameliorating glycemic control, decreasing insulin dependency, and augmenting native β-cell performance in human studies (Hu et al., 2016; Bhansali et al., 2015; Dantas et al., 2021; Izadi et al., 2022; Lian et al., 2023).

Particularly compelling clinical documentation includes a landmark case demonstrating insulin autonomy following transplantation of endoderm stem cell-derived islet tissue in a type 2 diabetic individual, providing validation for regenerative β-cell substitution strategies (Wu et al., 2024). Additionally, pancreatic progenitor cells derived from human pluripotent stem cells have advanced into clinical implementation, with encapsulated cellular products exhibiting glucose-dependent C-peptide release and durable glycemic enhancement (Keymeulen et al., 2024; Ramzy et al., 2021). Notwithstanding these promising outcomes, comprehensive comparative analyses directly assessing stem cell-based interventions versus established conventional treatment modalities, particularly regarding pancreatic β-cell functional restoration, remain sparse and dispersed throughout existing scientific literature.This systematic review aims to comprehensively evaluate and compare the effectiveness of stem cell therapy versus conventional therapy in improving pancreatic β-cell function in type 2 diabetes patients.

RESEARCH METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and methodological rigor throughout the review process.

Source of Information and Search Strategy

Source of information search was conducted in the following electronic databases: PubMed, Cochrane Library , Web of Science, and Scopus. Medical Subject Headings and free text terms used.

We searched relevant records from January 1, 2015 until October 20, 2025. Search strategy incorporated the following keywords: ("diabetes mellitus type 2" OR "type 2 diabetes" OR "T2DM") AND ("stem cell" OR "mesenchymal stem cell" OR "cell therapy" OR "cell-based therapy" OR "stromal vascular fraction") AND ("beta cell" OR "C-peptide" OR "insulin secretion" OR "endocrine function" OR "glycemic control" OR "HbA1c") AND (clinical OR "human trial" OR "randomized controlled trial" OR "intervention study"). Information on studies in progress was sought by searching ClinicalTrials.gov. Full search strategy can be seen in Supplementary Table S1.

Eligibility Criteria

Researchers screened and assessed the search results independently. The inclusion criteria included: (1) adult patients aged 20-65 years with HbA1c >6.5% diagnosed with type 2 diabetes mellitus; (2) stem cell therapy administered via intravenous, local, or combined routes; (3) comparison with conventional therapy or placebo; (4) randomized controlled trials (RCTs) or cohort studies, either prospective or retrospective; (5) outcome measures including pancreatic β-cell function (C-peptide, HOMA-β), glycemic control (HbA1c, fasting glucose), or adverse events; (6) full-text articles available in English.

Conference proceedings were deemed acceptable for inclusion provided they contained sufficient outcome information. When multiple reports originated from the same patient cohort, priority was given to the most current publication offering complete datasets. Any conflicts or divergent opinions between reviewers were reconciled through collaborative discussion until reaching mutual agreement.

Quality of Study Assessments

Two independent researchers conducted methodological quality appraisal of included studies according to their respective design types. Studies employing randomized controlled trial (RCT) designs were evaluated using RevMan 5.4.1 software, examining domains including concealment of allocation procedures (selection bias), masking of study participants and research staff (performance bias), blinding during outcome measurement (detection bias), management of missing data (attrition bias), and evidence of selective outcome reporting (reporting bias).

Management of Data

Retrieved citations were imported into reference management platforms such as Zotero to facilitate structured organization. Redundant entries were identified and removed through combined software-assisted detection and manual inspection processes. Two independent assessors screened titles and abstracts to identify potentially eligible investigations. Following initial screening, these assessors evaluated complete manuscripts of promising candidates to implement predetermined eligibility requirements.

Data Extraction

We extracted data on pancreatic β-cell function markers (C-peptide levels, HOMA-β, disposition index), glycemic control parameters (HbA1c percentage, fasting plasma glucose), insulin requirements, and adverse event rates. Other data included study characteristics, patient demographics, intervention protocols, and follow-up duration. When disagreements arose, a third reviewer participated in discussions and mediated to reach a consensus.

RESULTS AND DISCUSSION

Data identification

A comprehensive search was conducted across PubMed, Cochrane Library , Web of Science, and Scopus which yielded a total of 125 records. After removing 57 duplicates, 68 unique records remained for screening. During the title and abstract screening phase, 68 records were assessed, of which 45 were excluded due to irrelevance. This left 23 articles for full-text review. Of these, there were 6 articles were excluded due to studies reports not in full text. A total of 17 studies met the inclusion criteria. Six Studies excluded because outcome not comparing intervention with placebo and 5 studies not showing outcome clearcly. All of 6 studies after exclusion were further included in the systematic review (Figure 1).

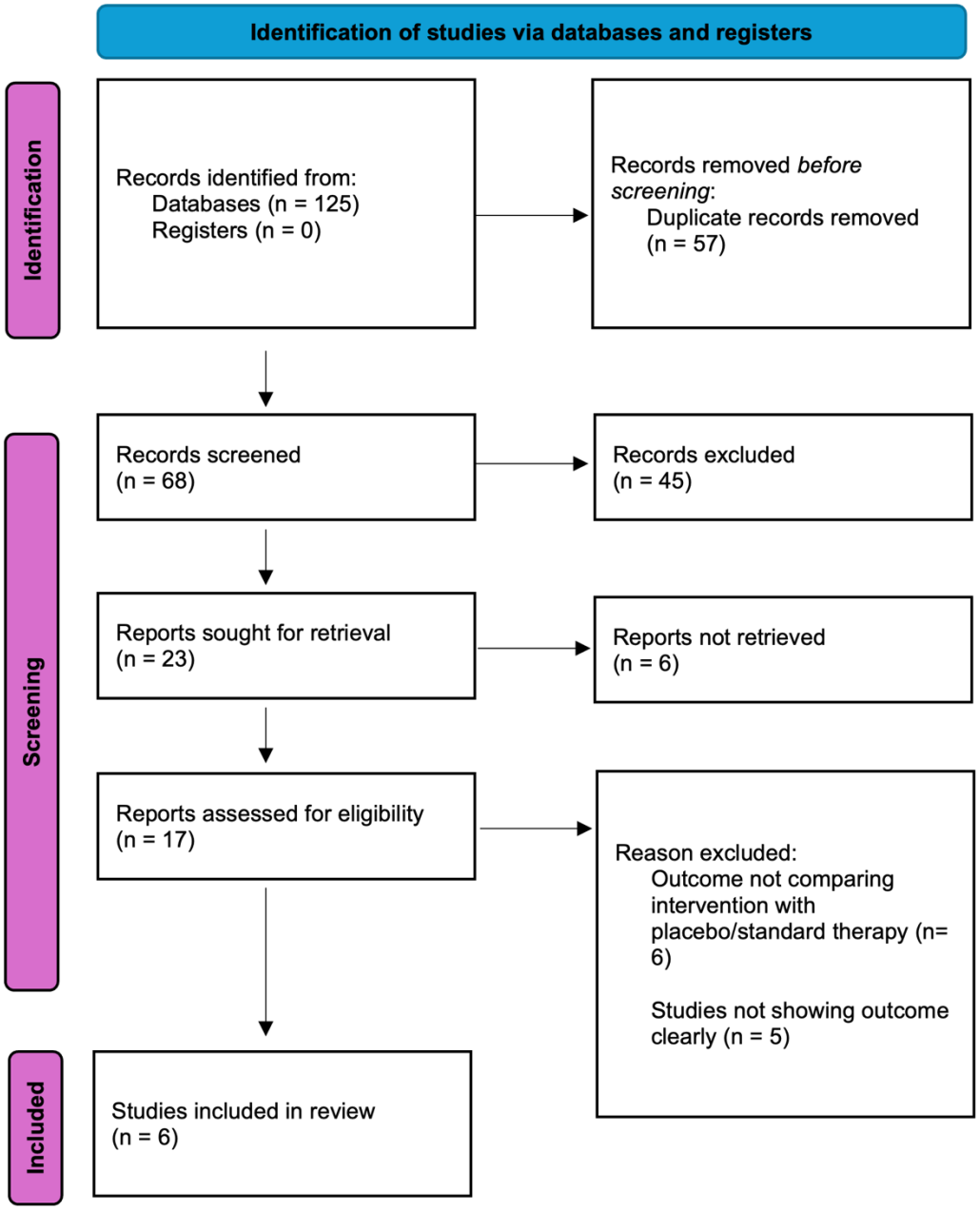

Figure 1. Study Selection using PRISMA 2020

Study characteristics and Risk of Bias Assessment

Six RCTs comprising 339 patients met the inclusion criteria (see Table 1). Studies enrolled adults with type 2 diabetes aged 44.5 to 59 years, with follow-up durations ranging from 12 weeks to 48 months. Stem cell sources varied and included autologous bone marrow-derived mesenchymal stem cells, allogeneic mesenchymal precursor cells, and umbilical cord-derived mesenchymal stem cells. Administration routes comprised intra-arterial injection via pancreatic arteries or intravenous infusion at the elbow vein, with intervention protocols employing single or repeated administrations at 4-week intervals (Skyler et al., 2015; Hu et al., 2016; Bhansali et al., 2017; Estrada et al., 2019; Zang et al., 2022, 2023). These differences in cell source, administration route, dose, and follow-up duration substantially limit direct cross-study comparability

Table 1. Characteristics of Included Studies

Study (Author, year)	Study Design	Total Sample	Total IG Sample	Total CG Sample	Age	Stem Cell Source	Intervention	Route of Administration	Follow Up Duration
Bhansali et al., 2017	RCT	30	ABM-MSC group: 10 ABM-MNC group: 10	Placebo: 10	ABM-MSC group: 50.5 ABM-MNC group: 44.5 Placebo: 53.5	Autologous bone marrow-derived mesenchymal stem cells (MSCs) and mononuclear cells (MNCs)	Autologous bone marrow	Intra-arterial injection via superior pancreatico-duodenal (SPD) artery (or splenic artery if anatomical variation)	12 months
Estrada et al., 2019	RCT	23	13	Standard Therapy: 10	IG : 59 ± 9 CG: 59 ± 6	Autologous bone marrow-derived stem cells (buffy coat fraction containing EPCs and few MSCs)	Autologous bone marrow (iliac crest)	Intra-arterial infusion into the dorsal pancreatic artery	12 months
Skyler et al., 2015	RCT	61	45	16	57.2 ± 7.9	Allogeneic mesenchymal precursor cells (MPCs, rexlemestrocel-L)	Adult bone marrow from healthy donors (STRO-3 immunoselected)	Intravenous (IV) infusion (single administration)	12 weeks primary; extended 2-year safety follow-up
Zang et al., 2023	RCT	73	37	36	UC-MSCs: 50.97 ± 8.63 Placebo: 50.53 ± 8.33	Umbilical cord-derived mesenchymal stem cells (UC-MSCs)	Human umbilical cord (Wharton's jelly)	Intravenous infusion at elbow vein, 3 times at 4-week intervals	12 months
Zang et al., 2022	RCT	91	45	46	UC-MSCs: 50.00 ± 9.38 Placebo: 50.45 ± 8.03	Mesenchymal Stem Cells (MSCs)	Umbilical Cord (UC-MSCs)	Intravenous infusion at elbow joint, three times with 4-week intervals	48 weeks
Hu et al., 2016	RCT	61	31	30	WJ-MSCs : 52.43 ± 4.88 Basal Treatment: 53.21 ± 8.22	Mesenchymal Stem Cells (MSCs)	Wharton's Jelly (umbilical cord)	Intravenous infusion (twice with 4-week interval)	36 months

Table 2. Outcomes of Included Studies

Study (Author, year)	C-Peptide	Stimulated C-Pep	HOMA-β	HbA1c	FPG	Insulin Requirement	Intervention Adverse Event
Bhansali et al., 2017	ABM-MSCs: 0.4 (0.4-0.5)	ABM-MSCs: 0.4(0.4-0.5)	ABM-MSCs: 61.8(49.3-77.4)	ABM-MSCs: 6.4(6.0-7.1)	ABM-MSCs: 6.7(6.4-6.7)	ABM-MSCs: 24.0(12.0-33.0)	NR
	ABM-MNCs: 0.7(0.4-1.1)	ABM-MNCs: 1.1(0.7-1.7)	ABM-MNCs: 86.2(53.7-101.3)	ABM-MNCs: 7.0(6.7-7.5)	ABM-MNCs: 6.5(6.2-6.7)	ABM-MNCs: 38.0(24.3-41.5)	NR
	Placebo: 0.7(0.4-0.9)	Placebo: 0.9(0.8-1.2)	Placebo: 88.9(54.2-120.9)	Placebo: 6.1(6.0-6.8)	Placebo: 6.3(5.5-6.7)	Placebo: 45.0(26.3-67.5)	NR
Estrada et al., 2019	IG: 1.9 ± 1.0	NR	NR	IG : 6.7 ± 1.0	NR	IG : 17.8 ± 13.6	NR
	CG: 0.7 ± 0.4	NR	NR	CG: 8.2 ± 1.0	NR	CG: 29.4 ± 11.3	NR
Skyler et al., 2015	0.3×10^6/kg: 3.590 ± 1.118	NR	NR	NR	0.3×10^6/kg: 10.8 ± 3.7	NR	NR
	1.0×10^6/kg: 4.201 ± 1.583	NR	NR	NR	1.0×10^6/kg: 11.0 ± 1.7	NR	NR
	2.0×10^6/kg: 3.599 ± 1.507	NR	NR	NR	2.0×10^6/kg: 9.2 ± 2.2	NR	NR
	Placebo: 3.965 ± 1.586	NR	NR	NR	Placebo: 10.0 ± 3.1	NR	NR
Zang et al., 2023	UC-MSCs: 2.07 ± 0.70	NR	NR	UC-MSCs: 7.52 ± 1.07	NR	NR	NR
	Placebo: 1.86 ± 0.60	NR	NR	Placebo: 8.19 ± 1.02	NR	NR	NR
Zang et al., 2022	UC-MSCs: 2.07 ± 0.70	UC-MSCs: 1.92 ± 0.53	NR	UC-MSCs: 7.52 ± 1.07	NR	UC-MSCs: 34.51 ± 20.19	Cerebral infarction (1/45)
	Placebo: 1.86 ± 0.60	Placebo: 1.81 ± 0.29	NR	Placebo: 8.19 ± 1.02	NR	Placebo: 45.19 ± 21.21	Femoral neck fracture caused by accident (1/45)

Note : NR = not reported

Risk of bias evaluation using the Cochrane RevMan 5.4.1 tool revealed generally acceptable methodological quality across the included studies (see Figures 2 and 3). Most trials demonstrated low risk for random sequence generation and allocation concealment. However, several studies exhibited unclear or high risk regarding blinding of participants and personnel, reflecting inherent challenges in stem cell intervention blinding. Incomplete outcome data and selective reporting showed predominantly low risk, though one study presented unclear risk for attrition bias. Overall, the included trials maintained reasonable internal validity despite methodological limitations common to regenerative medicine research. All sumarized for quality assessment can be seen on Supplementary Table S2.

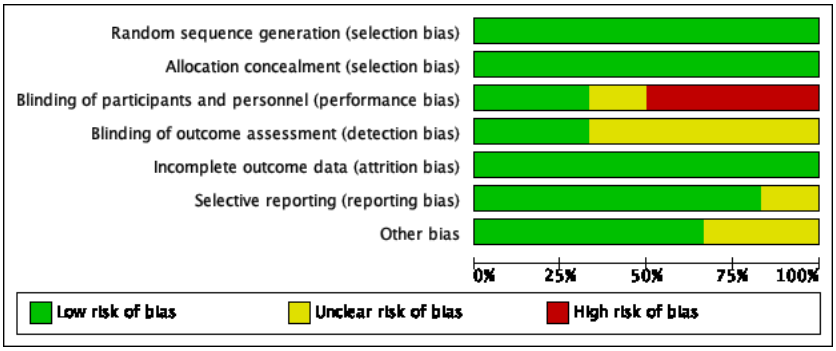

Figure 2. Risk of Bias Graph using RevMan 5.4.1

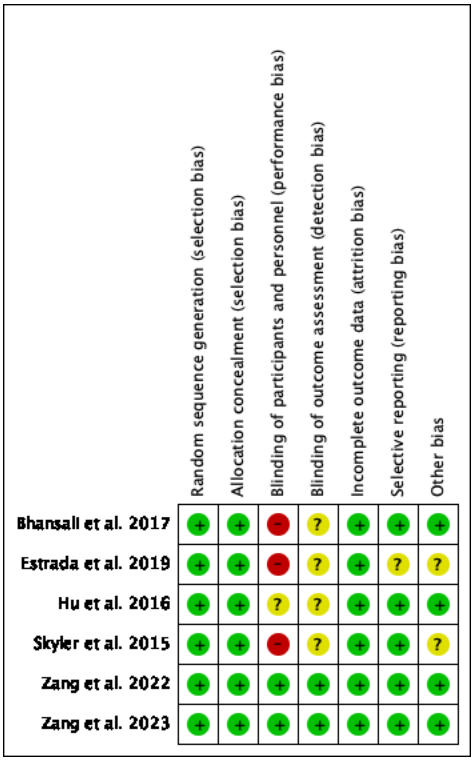

Figure 3. Risk of bias summary using RevMan 5.4.1

Study results

C-Peptide

Consistently variability characterized fasting C-peptide measurements among included studies (Table 2). Trials utilizing umbilical cord-derived mesenchymal stem cells showed

divergent patterns: Zang documented marginal increases in treatment arms (2.07±0.70 ng/mL) relative to control groups (1.86±0.60 ng/mL), whereas Estrada observed marked enhancement in intervention recipients (1.9±1.0 ng/mL) against control participants (0.7±0.4 ng/mL). Conversely, Bhansali's investigation employing autologous bone marrow-derived mesenchymal stem cells revealed diminished concentrations (0.4 ng/mL) when compared with both mononuclear cell recipients (0.7 ng/mL) and placebo-treated subjects (0.7 ng/mL). Notably, Skyler's trial examining allogeneic mesenchymal precursor cells at varying dosages demonstrated consistent measurements spanning 3.59-4.20 ng/mL across intervention cohorts, approximating placebo values (3.97 ng/mL).

Stimulated C-Peptide

Comprehensive evaluation of stimulated C-peptide concentrations proved challenging due to sparse data availability, with measurements reported in merely two investigations. Zang's 2022 investigation employing umbilical cord mesenchymal stem cells revealed negligible disparities between treatment recipients (1.92±0.53 ng/mL) and control participants (1.81±0.29 ng/mL), indicating minimal therapeutic differentiation. In contrast, Bhansali documented variable responses across intervention arms: mononuclear cell recipients achieved 1.1 ng/mL, placebo-treated subjects reached 0.9 ng/mL, while autologous bone marrow mesenchymal stem cell groups exhibited lower concentrations at 0.4 ng/mL. This insufficient reporting across analyzed trials fundamentally constrains rigorous evaluation of β-cell functional capacity through this critical parameter.

HOMA-β Index

Evaluation of HOMA-β indices remained severely restricted, as only Bhansali's investigation incorporated this outcome measure. Mononuclear cell recipients and placebo-treated participants demonstrated comparable functional indices at 86.2 (53.7-101.3) and 88.9 (54.2-120.9), respectively, whereas autologous bone marrow mesenchymal stem cell groups exhibited notably reduced values of 61.8 (49.3-77.4). However, interpretation of these diminished indices in stem cell recipients as indicative of inferior β-cell function carries substantial uncertainty, given the considerable overlap in confidence intervals and unavailability of pre-treatment baseline measurements. This singular source of HOMA-β data among analyzed studies fundamentally prevents generalized inferences concerning stem cell interventions' impact on pancreatic insulin secretory function.

Glycated Hemoglobin (HbA1c)

Glycemic control assessment through HbA1c measurements revealed heterogeneous therapeutic responses across four investigations. The most pronounced improvement emerged in Estrada's cohort, where stem cell-treated patients achieved 6.7±1.0% compared with 8.2±1.0% in standard therapy recipients. Umbilical cord mesenchymal stem cell administration in Zang's trials consistently produced favorable outcomes, reducing HbA1c to 7.52±1.07% against placebo values of 8.19±1.02%. Paradoxically, Bhansali documented superior glycemic indices in placebo-treated subjects (6.1%) relative to both autologous bone marrow

mesenchymal stem cell recipients (6.4%) and mononuclear cell groups (7.0%), likely attributable to pre-treatment patient characteristic disparities. Collectively, stem cell-based interventions demonstrated predominantly favorable glycemic modulation, although therapeutic magnitude exhibited substantial variation contingent upon cellular origin and delivery methodologies.

Fasting Plasma Glucose

Only two trials provided fasting plasma glucose measurements, substantially restricting systematic analysis of this metabolic parameter. Negligible variation characterized Bhansali's multi-arm comparison, where autologous bone marrow mesenchymal stem cells, mononuclear cells, and placebo groups demonstrated comparable concentrations at 6.7 mmol/L, 6.5 mmol/L, and 6.3 mmol/L, respectively. In contrast, Skyler's dose-ranging investigation of allogeneic mesenchymal precursor cells reported fasting glucose values between 9.2±2.2 mmol/L and 11.0±1.7 mmol/L across treatment cohorts, with control participants at 10.0±3.1 mmol/L. This paucity of available data combined with divergent findings across studies precludes definitive characterization of stem cell therapy's impact on fasting glycemic control.

Insulin Requirements

All trials providing insulin dosage data demonstrated consistent therapeutic advantages favoring stem cell interventions. The most substantial dose reduction emerged in Bhansali's cohort, where autologous bone marrow mesenchymal stem cell recipients required merely 24.0 units daily versus 38.0 units for mononuclear cells and 45.0 units for placebo-treated subjects. Comparable insulin-sparing patterns appeared in Estrada's study (stem cells: 17.8±13.6 units; controls: 29.4±11.3 units) and Zang's umbilical cord mesenchymal stem cell trial (intervention: 34.51±20.19 units; placebo: 45.19±21.21 units). While these cumulative findings suggest meaningful exogenous insulin dose-lowering potential with stem cell therapies, marked inter-individual variability in therapeutic response persisted throughout analyzed studies.

Adverse Events

Adverse event data were absent or categorized as not reported in five of six included trials. The absence of reported adverse events should not be interpreted as evidence of safety; it more likely reflects inadequate surveillance and inconsistent reporting standards across studies. Zang et al. (2022) provided the only systematic safety data, reporting one cerebral infarction in a stem cell recipient (1/45) and one accidental femoral neck fracture in the placebo group (1/45), both determined to be unrelated to study interventions. Skyler et al. (2015) reported no acute or serious adverse events, no serious hypoglycemia, and no donor-specific anti-HLA sensitization over 12 weeks. Long-term safety profiles, particularly regarding immunological sequelae, remain uncharacterized in the available evidence base.

Discussion

Evidence synthesis from six randomized controlled trials involving 339 participants evaluated stem cell-based interventions against standard approaches for pancreatic β-cell functional restoration in type 2 diabetes. Convergent outcomes across multiple parameters revealed generally advantageous, albeit heterogeneous, therapeutic responses. Notable fasting C-peptide enhancement emerged in Estrada et al. (2019), demonstrating nearly threefold elevation in stem cell recipients (1.9±1.0 ng/mL) compared with control subjects (0.7±0.4 ng/mL), signifying substantially improved endogenous insulin secretory capacity. Parallel findings appeared in Zang et al. (2022, 2023), consistently documenting mean HbA1c reductions of 0.67% relative to placebo cohorts. Insulin dosage requirements declined markedly throughout reporting trials, with Bhansali et al. (2017) recording 46.7% reduction in daily exogenous insulin needs (24.0 versus 45.0 units). These observations are consistent with the hypothesis that stem cell interventions may influence β-cell pathological processes in type 2 diabetes, though the heterogeneity of the included studies and the descriptive nature of this synthesis preclude causal conclusions. The cumulative evidence suggests regenerative interventions may offer disease-modifying potential beyond symptomatic glucose management achieved through traditional medical approaches.

Biological plausibility underlying observed clinical improvements aligns extensively with preclinical and translational investigations demonstrating mesenchymal stem cells' multifaceted regenerative properties. Comprehensive reviews by Bayat et al. (2024) and Habiba et al. (2024) documented MSCs' therapeutic mechanisms encompassing paracrine signaling, immunomodulatory effects, and direct transdifferentiation into insulin-secreting cells. MSCs release growth factors including vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-1, collectively promoting endogenous β-cell survival, proliferation, and functional recovery (Li et al., 2016; Aringazina et al., 2025). Additionally, immunomodulatory capabilities mitigate chronic inflammatory processes characteristic of type 2 diabetes pathophysiology, reducing cytokine-mediated β-cell death (Cho et al., 2018; Shalaby & Abdelalim, 2020). Wu et al. (2024) reported insulin independence following personalized endoderm stem cell-derived islet transplantation in a type 2 diabetes patient, offering preliminary evidence for regenerative β-cell replacement, though study limitations and the single-case nature of the report preclude broader generalization. Keymeulen et al. (2024) similarly demonstrated glucose-responsive C-peptide secretion from encapsulated stem cell-derived β-cells in type 1 diabetes patients, suggesting translational potential across diabetes subtypes. Ramzy et al. (2021) corroborated sustained glycemic control following pluripotent stem cell-derived pancreatic endoderm implantation. This mechanistic convergence with clinical outcomes validates stem cell therapy as potentially disease-modifying rather than purely symptomatic intervention.

Notwithstanding predominantly favorable outcomes, critical contradictory results warrant careful interpretation. Bhansali et al. (2017) paradoxically reported diminished HOMA-β indices in autologous bone marrow MSC recipients (61.8) versus placebo groups (88.9), contradicting anticipated β-cell secretory capacity improvements. Multiple explanatory factors merit consideration. Baseline heterogeneity likely influenced outcomes, as inadequate baseline

HOMA-β documentation potentially reflected pre-existing residual β-cell function disparities rather than genuine treatment effects (Matthews et al., 2023; Serbis et al., 2023). Administration route differences—Bhansali's intra-arterial pancreatic artery delivery versus Zang et al. (2022, 2023) and Hu et al. (2016) intravenous approaches—may fundamentally affect MSC homing, engraftment efficiency, and functional integration (Ghoneim et al., 2024; Feng et al., 2024). Autologous bone marrow-derived MSCs potentially exhibit compromised proliferative capacity and paracrine potency compared with younger umbilical cord sources, particularly in elderly patients with prolonged diabetes duration where cellular senescence and metabolic memory impair stem cell functionality (Ogieuhi et al., 2025; Dantas et al., 2021). HOMA-β calculation methodology demonstrates substantial variability, inadequately capturing dynamic insulin secretion patterns in patients with preserved yet dysfunctional β-cells exhibiting delayed first-phase responses (Khin et al., 2023; Weir & Bonner-Weir, 2004). Furthermore, Skyler et al. (2015) documented absent dose-response relationships across allogeneic MPC doses ($0.3\text{-}2.0\times10^6$/kg), suggesting threshold effects or qualitative cellular characteristics predominate over quantitative relationships.

Distinguishing therapeutic mechanisms between stem cell interventions and conventional diabetes pharmacotherapy contextualize clinical implications. Traditional agents—metformin, sulfonylureas, exogenous insulin—predominantly achieve glycemic regulation through insulin sensitization, secretagogue stimulation of residual β-cells, or hormonal supplementation, without fundamentally reversing progressive β-cell depletion (Baker et al., 2021; Kalyani et al., 2025; Petrie et al., 2024). This limitation manifests clinically as treatment inadequacy rates approaching 50% within three years and 75% within nine years, necessitating continuous therapeutic intensification (Matthews et al., 2023). Conversely, stem cell therapy addresses pathophysiological foundations through regenerative pathways: replacing depleted β-cell mass, protecting surviving cells from oxidative and inflammatory damage, and potentially reversing glucotoxicity-induced dysfunction (Eguchi et al., 2021; Cerf, 2013; Almaça et al., 2020). Skyler's dose-escalation investigation provided valuable safety data across dosing tiers, though failed establishing clear dose-response efficacy, indicating optimal protocols remain undefined (Skyler et al., 2015). Regarding durability, Hu et al. (2016) documented sustained improvements extending 36 months post-intervention, representing longest follow-up among included studies and suggesting potential disease-modifying effects beyond transient symptomatic relief. Zang's 0.67% mean HbA1c reduction exceeds 0.5% thresholds generally considered clinically meaningful for reducing diabetic complications (American Diabetes Association, 2024; International Diabetes Federation, 2023). Consistent insulin-sparing effects hold particular clinical relevance, potentially improving patient quality of life, decreasing hypoglycemic risk, and mitigating insulin-induced weight gain (DeFronzo & Abdul-Ghani, 2011).

Multiple methodological constraints limit the drawing of definitive conclusions from current evidence. Sample sizes remained modest (23-91 participants per trial), substantially underpowering statistical analyses and precluding subgroup exploration by diabetes duration, baseline β-cell reserve, or patient phenotypes (Bhansali et al., 2017; Estrada et al., 2019; Skyler et al., 2015; Zang et al., 2022, 2023; Hu et al., 2016). Follow-up periods predominantly spanned

merely 12 months, with Hu's 36-month observation representing notable exception, leaving long-term efficacy, durability, and safety profiles incompletely characterized (Lian et al., 2023; Izadi et al., 2022). Risk of bias evaluation revealed concerning inadequacies in participant and personnel masking across multiple trials, introducing potential performance and detection biases potentially inflating treatment effect estimates, particularly for subjective outcomes like insulin dosing adjustments. Substantial protocol heterogeneity further complicates interpretation: cell sources varied across autologous bone marrow, allogeneic bone marrow, and umbilical cord derivations; administration routes differed between intra-arterial and intravenous; dosing ranged $0.3\text{-}2.0\times10^6$ cells/kg; treatment schedules employed single versus repeated infusions at variable intervals (Aringazina et al., 2025; Bayat et al., 2024). This heterogeneity precludes pooled quantitative meta-analysis and obscures optimal therapeutic parameter identification. Publication bias constitutes additional concern, as no large-scale negative trials were identified despite interventions' experimental nature, suggesting selective reporting favoring positive results (Ioannidis, 2016). Most critically, adverse event documentation proved grossly inadequate, with five of six trials designating safety outcomes "not reported" (Habiba et al., 2024). The absence of reported adverse events should not be interpreted as evidence of safety, as it more likely reflects inadequate surveillance and inconsistent reporting standards, which fundamentally precludes any reliable safety conclusion from the current evidence base.

Critical knowledge deficits necessitate targeted investigation advancing clinical translation. No head-to-head comparative trials directly evaluate different stem cell sources—autologous versus allogeneic, bone marrow versus umbilical cord versus adipose-derived—leaving optimal cellular product unidentified (Ghoneim et al., 2024; Feng et al., 2024). Dose-finding remains empirical rather than evidence-based, with Skyler's dose-escalation study failing to establish dose-response relationships, suggesting current strategies may be suboptimal or therapeutic effects depend on qualitative cellular characteristics rather than quantitative parameters (Skyler et al., 2015; Ogieuhi et al., 2025). Long-term safety surveillance beyond five years remains absent, precluding late complication assessment including tumorigenicity, ectopic tissue formation, or immunological sequelae (Shalaby & Abdelalim, 2020; Li et al., 2016). No cost-effectiveness analyses exist despite likely substantial cellular manufacturing expenses (World Health Organization, 2022). Patient selection criteria remain undefined, with current trials enrolling broad populations without stratification by disease duration, residual β-cell function, or diabetes phenotype (Weir & Bonner-Weir, 2004; Khin et al., 2023). Current evidence suggests promising but preliminary efficacy, with consistent benefits across C-peptide levels, HbA1c reduction, and insulin-sparing effects. However, substantial outcome heterogeneity, limited follow-up, inadequate safety surveillance, and methodological constraints prevent endorsement for widespread adoption outside investigational contexts. Mechanistic rationale remains compelling (Wu et al., 2024; Keymeulen et al., 2024; Ramzy et al., 2021), yet premature clinical integration would be unwarranted given unresolved questions regarding optimal protocols, durability, safety, and cost-effectiveness.

CONCLUSION

Stem cell-based therapeutic approaches exhibit encouraging capacity for enhancing pancreatic β-cell functional performance in type 2 diabetes populations, as demonstrated through improved C-peptide secretion, glycemic control optimization reflected in HbA1c decreases, and substantial reductions in daily insulin requirements versus traditional pharmacological interventions. The biological rationale underlying potential disease modification remains scientifically persuasive. However, application should remain restricted to well-structured clinical trial frameworks until rigorous investigations clarify optimal therapeutic protocols, define appropriate patient selection parameters, establish durability of therapeutic responses, and comprehensively characterize benefit-risk profiles through systematic evaluation.

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Author Contributions

M.S. make outline and also design the study, make the literature search, and drafted the manuscript. M.R.S. supervised methodological. A.E.D. make data extraction, assisted analysis, and revised the manuscript. All authors reviewed the final version.

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Ethical Statement

This study not involve direct contact with human participants or the collection of primary data.

Declaration of Interest

The authors declare no conflicts of interest and otherwise.

Data Sharing Statement

All data supporting this study are from previous articles included in the review. Extracted datasets are available from the corresponding author by request.

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