https://doi.org/10.46389/rjd-2026-2155
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2026; volume 33, issue 1, pages 114–127

Review

Cellular therapy in the management of diabetes mellitus: a meta-analysis

Cosmin Sandu [1] *

[1] Department of Radiology, Bihor County Emergency Clinical Hospital, Faculty of Medicine, University of Oradea, Oradea, Romania

* Correspondence to: Sandu Cosmin, Department of Radiology, Bihor County Emergency Clinical Hospital, Faculty of Medicine, University of Oradea, Gheorghe Doja Street, no. 65-67, 410169, Ordea, Bihor, Romania. Phone: +40751964196; E-mail: sanducosmin150@gmail.com

Received: 16 January 2026 / Accepted: 19 February 2026

Abstract

Diabetes mellitus can be considered a modern-day epidemic that is treatable but not curable with current therapeutic approaches. This study aimed to evaluate whether stem cell transplantation could represent an alternative treatment strategy with curative potential. In March 2025, a comprehensive literature review was conducted across 10 databases. Relevant studies were selected and their results were synthesized through meta-analysis. Outcomes were categorized into two domains: metabolic and secretory. The metabolic outcome showed a mean decrease in glycated hemoglobin of 0.937, while the secretory outcome demonstrated a mean increase in C-peptide secretion of 0.649; however, the latter did not reach statistical significance. These findings suggest that stem cell therapy exerts a therapeutic effect in patients with diabetes, although the magnitude of this effect is insufficient to support its role as a curative therapy. The observed benefits are most likely mediated by paracrine mechanisms rather than by the differentiation of stem cells into insulin-secreting cells.

Keywords: diabetes mellitus, stem cells, transplantation, glycated hemoglobin, polypeptide C

Introduction

Diabetes mellitus is defined as a complex pathology—a heterogeneous syndrome characterized by the progressive deterioration of glycemic homeostasis, with severe consequences for the entire organism. It is treatable but not curable and is increasingly becoming a major public health challenge affecting all levels of care due to its rising prevalence in the general population [1, 2].

In addition to the well-established classification of this disease into multiple types, which highlights differences in etiology and pathophysiology, it must also be considered that within each of these subtypes the patient cohort is highly heterogeneous, with variations in age, disease stage, and associated complications [3]. This represents a major challenge in the current context of so-called universal therapy, which, with relative variations depending on the type of diabetes, is based on the use of oral antidiabetic agents and insulin replacement to maintain glycemic control. Technological developments that have enabled the creation of sensor-augmented insulin pumps—capable of maintaining glycemic values within the normal range for 59±14% of the time—or artificial pancreas systems, which achieve the same for 71±12% of the time, have marked a turning point in improving the quality of life of patients with diabetes, but they also come with significant disadvantages [4].

The next therapeutic step, available only in certain regions of the world and more closely aligned with the principles of personalized medicine, is pancreatic islet transplantation. This approach is associated with other major disadvantages, namely extremely limited availability and highly advanced technological complexity, which severely restrict its clinical applicability [4].

As a result of recent advances in medical sciences, another emerging therapeutic possibility may involve

the use of stem cells. Cell therapy has not yet become established as a standard intervention in routine medical practice and remains under investigation. Further research is required regarding the route of administration, cell type, dosage, and mechanisms of action. Although it was initially believed that stem cells might have the capacity to convert into insulin-secreting cells *in vivo*, this hypothesis has not yet been supported by clear evidence [5]. On the other hand, studies have demonstrated the possibility of *in vitro* differentiation of human multipotent cells into glucose-responsive cells with a genotype similar to that of β cells, as well as their ability to induce diabetes regression in mouse models [6, 7].

Nevertheless, what would be the mechanism by which a stem cell transplant could influence the course of diabetes in humans? Beyond the still unproven possibility of direct differentiation into pancreatic β cells, attention has also been drawn to their potential to replace pre-existing pancreatic precursor cells with improper differentiation or to influence these cells through paracrine effects, thereby directing their differentiation [8]. It is widely accepted that, in both type I diabetes—an eminently inflammatory disease driven by autoimmune mechanisms—and type II diabetes, inflammation plays a central role in the pathogenic process and in the development of insulin resistance [5]. Mesenchymal stem cells are known to exert strong anti-inflammatory and immunomodulatory effects through the cytokines they secrete. However, it remains unclear whether their influence on glycemic control is due to cellular protection, modulation of insulin resistance, or the induction of new cell formation [2, 8].

The present study aims to conduct a systematic review with meta-analysis of relevant studies on stem cell therapy in patients with diabetes mellitus, in order to assess the effect of this invasive procedure on patients' metabolic control compared with the use of therapies already well established in clinical practice. The central elements of interest focus on a meta-analytic evaluation of effects on metabolic control, quantified by HbA1c, and on secretory function, quantified by C-peptide levels.

Material and methods

Study design and search strategy

During February–March 2025, a systematic search was conducted across major databases representative of the medical literature, following the PICOTT methodology: Patients – individuals with diabetes mellitus of any type; Intervention – stem cell therapy; Comparison – standard therapy; Outcome – metabolic control (glycemia); Type of research question – therapeutic intervention; Type of studies – clinical trials [9].

An extensive search of the specialized literature was performed in accordance with the methodology presented in Table 1.

Eligibility criteria and study selection

Clinical trial papers published from 2015 onward and relevant to the research topic were selected. Eligible studies had to be written in English, investigate the use of stem cells of any functional or morphological category in patients with diabetes mellitus, be controlled trials, and have a JADAD score [10] of at least 3. In addition, studies were required to have a minimum follow-up period of 3 months and to report numerical values for the variables of interest (HbA1c or C-peptide) in the form of mean±standard deviation.

The search yielded approximately 1,500 records. After screening titles and abstracts, 34 studies relevant to the research topic were identified.

Data extraction

From the selected studies, manual data extraction was performed for the variables of interest, namely fasting C-peptide and HbA1c values, reported as mean and standard deviation. Studies reporting these data for at least one of the variables of interest were included in the statistical analysis. Studies in which the data were presented only in graphical form were processed using automeris.io [11] to extract numerical values. Studies that compared multiple patient cohorts using different cell types or varying cell concentrations were divided into multiple arms (Table 2).

Statistical analysis

The extracted data were organized in tabular format for the variables of interest using Excel, where mean values and basic descriptive statistics were calculated. Subsequently, part of the dataset was analyzed using MedCalc [12] to perform the meta-analysis. Results are reported as mean differences (MD) with 95% confidence intervals (CI) and are graphically represented using forest plots. Study heterogeneity was assessed using the Cochran Q test ($p<0.1$ was considered

Table 1: Methodology and terminology used in database searches.

Database		Searched terminology	Results
I.	PUBMED	[diabetes AND stem cell therapy AND glucose levels AND clinical trial]	30 Results → 8 studies
II.	Clinical trials. Gov	[Diabetes | stem cells | Outcome measure: Glucose Level Change]	17 Results → None of relevance
III.	Cochrane	[diabetes mellitus AND stem cell therapy AND glucose levels AND clinical trial]	21 Results → 3 studies 3 duplicates
IV.	Scopus	[diabetes AND stem AND cell AND therapy AND glucose AND levels AND clinical AND trial] - With a 10-year limite	69 Results → 12 studies 8 duplicates
V.	Biomed central Stem cell research and therapy	[Stem cell therapy for managing glucose in diabetic patients]	36 Results → None of relevance
VI.	BioMed central	["Stem cell therapy" for managing glucose in diabetic patients]	53 Results → None of relevance
VII.	Nature portfolio	[diabetes AND stem cell therapy AND glucose levels AND clinical trial]-filter research	229 Results → None of relevance 1 duplicate
VIII.	Science direct	["diabetes" AND "stem cell" therapy AND glucose levels AND clinical trial NOT review] Limited by a 10-year filter	432 Results → 5 studies 2 duplicates
IX.	Semantic Scholar	[diabetes AND stem cell AND glucose levels AND clinical trial NOT (review OR meta-analysis)] Limited by a 10-year filter with full PDF access	583 Results → 3 studies 9 duplicates
X.	Other sources	Excerpt from the citations of one of the studies found	1 study

indicative of statistical significance) and the I^2 statistic (I^2>50% was considered indicative of substantial heterogeneity) [13].

Results

Study selection and exclusion

Of the 34 studies initially identified, 7 studies met the eligibility criteria and were included in the data analysis, as shown in Figure 1.

The characteristics of the studies included in the analysis are presented in Table 2. The studies were conducted between 2015 and 2024 and included patients with type 1 diabetes (2 studies, 63 patients) and type 2 diabetes (5 studies, 343 patients). Umbilical cord–derived stem cells were used in 3 studies (97 patients), and bone marrow–derived mesenchymal stem cells were used in 4 studies (68 patients). In two studies, autologous mononuclear cells were additionally used, with one study including a cohort treated exclusively with these cells.

Accordingly, study 16 was divided into two branches: 16.1, investigating the combination of mesenchymal stem cells and bone marrow–derived mononuclear cells, and 16.2, investigating therapy with mononuclear cells alone.

Study 11 investigated the effects of three doses of allogeneic bone marrow–derived mesenchymal precursor cells compared with the same control; therefore, it was divided into three arms: 11.1 with 0.3×10^6 cells/kg, 11.2 with 1×10^6 cells/kg, and 11.3 with 2×10^6 cells/kg.

As shown in Table 2, the studies conducted by Esteban J. Estrada [8], Jinquan Cai [14], and Zhixian Wu [15] used a more invasive approach, involving the administration of stem cells via the dorsal pancreatic artery, aiming for administration as close to the site of action as possible. In contrast, the studies by Li Zang [2], Jianxia Hu [16], Jay S. Skyler [5], and Mahmoud Izadi [17] utilized an intravenous peripheral route for cell administration.

https://doi.org/10.46389/rjd-2026-2155

Table 2: Characteristics of the studies included in the final analysis.

Number in initial search	Reference	Notes on the protocol	Type of disease	Participants						Period of follow-up
				Control			Cases			
	Autor and year			No.	Age	BMI	No.	Age	BMI	
4	Esteban J. Estrada; 2019 [8]	An infusion of autologous stem cells into the dorsal pancreatic artery combined with hyperbaric oxygen therapy (10 sessions before and 10 after) plus standard pharmacological therapy *versus* standard therapy alone.	D2	10	59±6	23.1±2.5	13	59±9	27.0±4.0	1 year
5	Li Zang; 2022 [2]	Umbilical cord–derived mesenchymal stem cells administered intravenously three times at 4-week intervals at a dose of 1×10^6 cells/kg *via* the antecubital vein, plus standard therapy *versus* standard therapy plus placebo.	D2	46	50.45±8.03	28.13±3.04	45	50±9.38	28.69±3.35	48 weeks
9	Jianxia Hu; 2016 [16]	Mesenchymal stem cells derived from Wharton's jelly, administered intravenously at a dose of 1.0×10^6 cells/kg twice at 4-week intervals, plus standard therapy *versus* standard therapy plus placebo.	D2	30	53.21±8.22	27.03±6.68	31	52.43±4.88	26.74±5.41	36 months
10	Jinquam Cai; 2016 [14]	Umbilical cord–derived mesenchymal stromal stem cells (1.1×10^6 cells/kg) and autologous bone marrow–derived mononuclear cells (106.8×10^6 cells/kg) infused into the dorsal pancreatic artery, plus standard therapy *versus* standard therapy alone.	D1	21	-	22.06±2.46	21	-	21.99±1.78	1 year
11.1	Jay S Skyler; 2015 [5]	Allogeneic bone marrow–derived mesenchymal precursor cells, administered intravenously at a dose of 0.3×10^6 cells/kg, plus oral antidiabetic therapy *versus* oral antidiabetic therapy plus placebo.	D2	16	58.7±7.3	32.6±6.2	15	57.7±8.2	34.8±6.5	12 weeks
11.2	Jay S Skyler; 2015 [5]	Allogeneic bone marrow–derived mesenchymal precursor cells, administered intravenously at a dose of 1×10^6 cells/kg, plus oral antidiabetic therapy *versus* oral antidiabetic therapy plus placebo.	D2	16	58.7±7.3	32.6±6.3	15	55.3±11.4	34.4±4.7	12 weeks

Table 2: Continued.

Number in initial search	Reference	Notes on the protocol	Type of disease	Participants						Period of follow-up
				Control			Cases			
	Autor and year			No.	Age	BMI	No.	Age	BMI	
11.3	Jay S Skyler; 2015 [5]	Allogeneic bone marrow–derived mesenchymal precursor cells, administered intravenously at a dose of 2×10^6 cells/kg, plus oral antidiabetic therapy *versus* oral antidiabetic therapy plus placebo.	D2	16	58.7±7.3	32.6±6.4	15	57.2±6.6	32.4±4.5	12 weeks
16.1	Zhixian Wu; 2024 [15]	Mesenchymal stem cells (1×10^6 cells/kg) and bone marrow–derived mononuclear cells administered into the dorsal pancreatic artery, combined with mesenchymal stem cells administered intravenously (1×10^6 cells/kg) one week later, plus standard therapy *versus* standard therapy alone (with 8-year follow-up for diabetes-related complications).	D2	29	54.6±5.0	25.3±2.6	29	52.8±4.5	25.2±2.1	1 year
16.2	Zhixian Wu; 2024 [15]	Bone marrow–derived mononuclear cells administered into the dorsal pancreatic artery, plus standard therapy *versus* standard therapy alone (with 8-year follow-up for the incidence of diabetes-related complications).	D2	29	54.6±5.0	25.3±2.6	28	53.2±6.1	25.6±3.2	1 year
23	Mahmoud Izadi; 2022 [17]	Autologous bone marrow–derived mesenchymal stem cells in newly diagnosed patients (6 weeks prior to enrollment), administered intravenously in two doses of 1×10^6 cells/kg at weeks 0 and 3, plus insulin therapy *versus* insulin therapy plus placebo.	D1	10	11.5±2.63	18.91±3.41	11	10.27±1.67	16.75±2.57	1 year

https://doi.org/10.46389/rjd-2026-2155

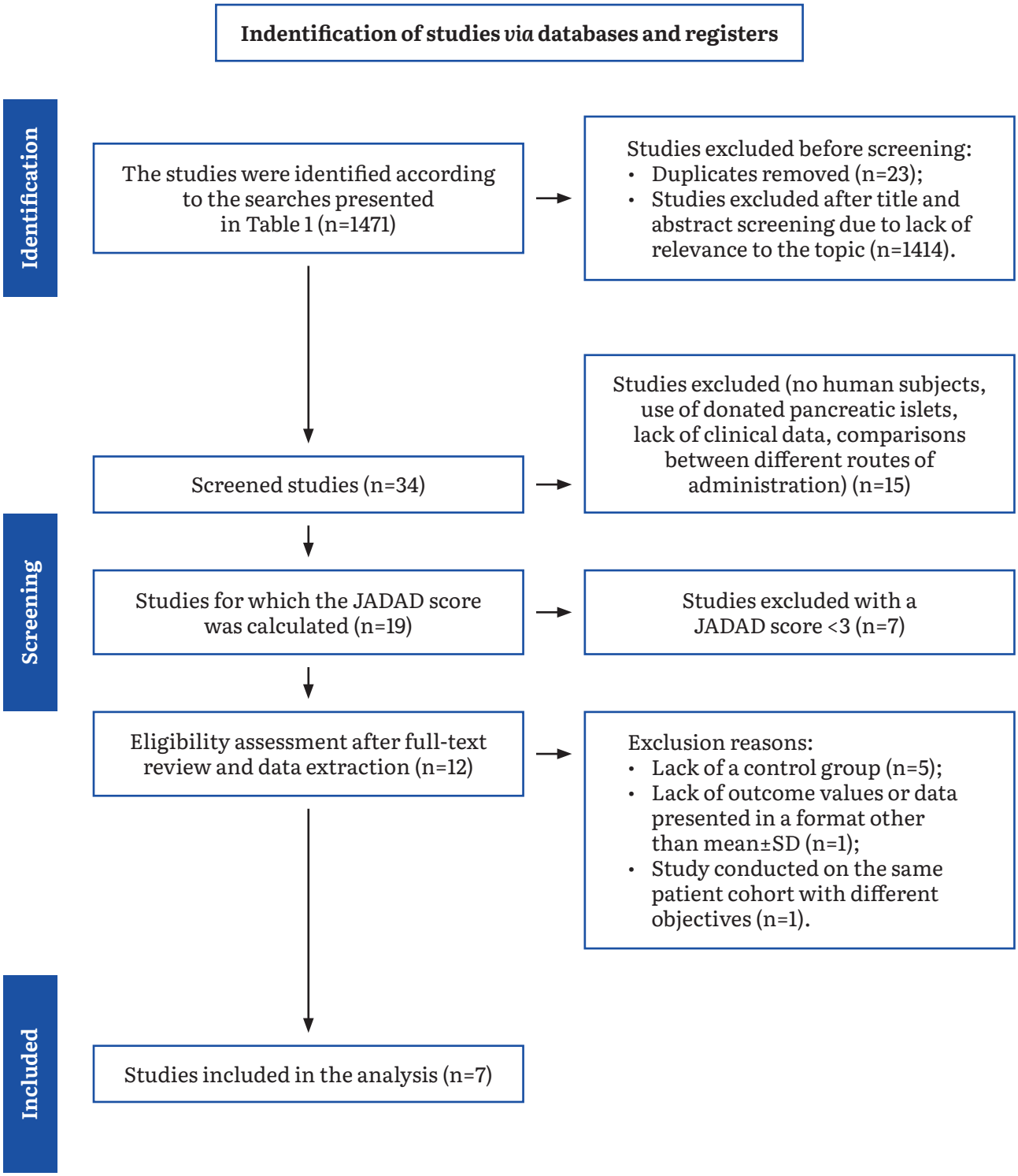

Figure 1: PRISMA flow diagram for study selection.

The follow-up period for the studies ranged from 12 weeks to 36 months.

The included studies were assessed for the possibility of publication bias using the RoB 2 tool [18]. The results are summarized in Figure 2.

As it can be observed, there are some concerns in 42.85% of the studies, primarily due to the inability to implement a blind study design. In such cases, patients could potentially modify their behavior depending on the group to which they were assigned, thereby substantially influencing diabetes control.

Metabolic outcome (HbA1c)

Glycated hemoglobin (HbA1c) is a non-enzymatic glycosylation product of hemoglobin in erythrocytes based

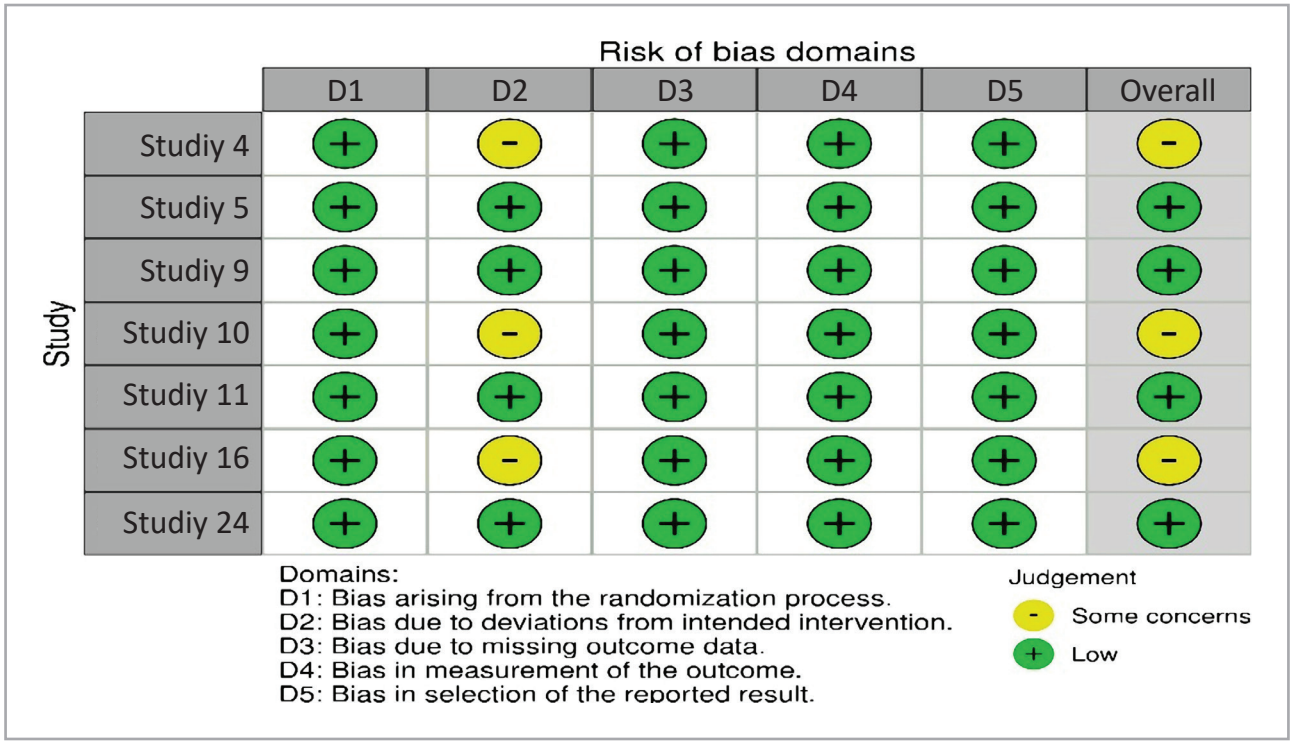

Figure 2: "Traffic light" table for risk of bias assessment.

on the patient's blood glucose levels and is expressed as a percentage of total hemoglobin. Given that the average lifespan of erythrocytes is approximately 120 days, HbA1c reflects glycemic control over the preceding three months, surpassing the limitations of individual variability in routine plasma glucose measurements [19]. This provides the rationale for requiring the selected studies to have a minimum follow-up duration of three months.

Six studies were included in the analysis of HbA1c changes. As shown in Table 3, study 16 (Zhixian Wu [15]) was divided into two arms due to the use of two different types of cellular therapies in two patient cohorts, as mentioned above, while study 11 (Jay S. Skyler [5]) could not be included in the analysis because the way the data were presented did not allow calculation of the mean and standard deviation for HbA1c.

Table 3: HbA1c values in the studies included in the analysis.

HbA1c %									
Study		**Year**	**No cases**	**Average cases**	**SD cases**	**No control**	**Average control**	**SD control**	**Statistical relevance**
4	Esteban J. Estrada [8]	2019	13	7.3	0.9	10	8	0.7	p=0.0366
5	Li Zang [2]	2022	45	7.52	1.07	46	8.19	1.02	p=0.0081
9	Jianxia Hu [16]	2016	31	7.22	0.86	30	8.19	0.85	p<0.05
10	Jinquam Cai [14]	2016	21	7.5	1.0	21	8.8	0.9	p<0.01
11.1	Jay S Skyler [5]	2015	15	CDNI	CDNI	16	CDNI	CDNI	
11.2	Jay S Skyler [5]	2015	15	CDNI	CDNI	16	CDNI	CDNI	
11.3	Jay S Skyler [5]	2015	15	CDNI	CDNI	16	CDNI	CDNI	
16.1	Zhixian Wu [15]	2024	29	6.7	1.3	29	8.4	1.2	p<0.05
16.2	Zhixian Wu [15]	2024	28	7.3	1.2	29	8.4	1.2	p<0.05
23	Mahmoud Izadi [17]	2022	11	8.16	0.95	10	8.60	2.72	p=0.043

Note: SD – standard deviation; CDNI – study data insufficient to calculate the format of interest.

https://doi.org/10.46389/rjd-2026-2155

A Test for heterogeneity

Q	8.9119
DF	6
Significance level	P=0.1786
I^2 (inconsistency)	32.67%
95% CI for I^2	0.00 to 71.41

B Publication bias

Egger's test	
Intercept	-0.004637
95% CI	-5.7991 to 5.7898
Significance level	P=0.9984
Begg's test	
Kendall's Tau	0.04762
Significance level	P=0.8806

C Funnel plot

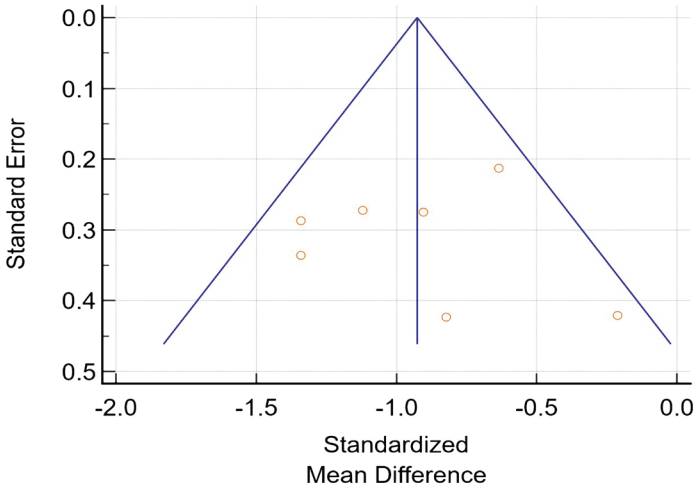

Figure 3: Statistical analysis of study heterogeneity and publication bias for HbA1c (A – Tests for heterogeneity; B – Publication bias; C – Funnel plot).

As it can be seen in the table, all included studies demonstrated a statistically significant reduction in HbA1c value.

The meta-analysis revealed moderate heterogeneity among the studies, with a Cochran's Q of 8.9119 (P>0.1) and an I^2 of 32.67%. These results indicate that a random-effects model should be used for the subsequent data analysis (Figure 3 A–C).

Although publication bias calculations were performed using Egger's and Begg's tests (Figure 3B), which indicate the absence of bias, these results cannot be considered conclusive because only seven studies were included in the analysis and the sample sizes of the patient cohorts were fewer than 50. The relatively symmetrical appearance of the studies in the funnel plot also suggests the absence of publication bias; however, this cannot be completely ruled out due to the limitations described above [13].

Further data analysis demonstrates a mean reduction of 0.937% in HbA1c, with a 95% confidence interval of −1.208 to −0.660 ($p<0.001$). This indicates that stem cell therapy can lead to an approximate one percent reduction in HbA1c in patients with diabetes mellitus (Figure 4 and Table 4).

C-peptide is the polypeptide cleaved from insulin and is secreted in equimolar amounts with it. Although a small portion is cleared by the liver, it is used in clinical practice to quantify patients' endogenous insulin secretion [20].

Six studies were included in the analysis of C-peptide effects. As shown in Table 5, study 11 (Jay S. Skyler [5]) was divided into three arms corresponding to the three patient cohorts receiving different doses (Table 5). For this study, data were reported as mean± standard deviation at baseline and as the change after 12 weeks in the same format. Since no correlation factor was provided, the post-therapy mean and standard deviation were calculated using the following formulas, assuming independence [13]:

- Post-therapy mean = Baseline mean + Change at 12 weeks;
- Post-therapy standard deviation = $\sqrt{[(\text{Baseline SD})^2 + (\text{SD of change at 12 weeks})^2]}$.

Additionally, study 16 (Zhixian Wu [15]) could not be included in the analysis due to the absence of values of interest. As shown in the table, the trend in C-peptide after stem cell therapy in patients with diabetes is ambivalent. The studies show both increases and

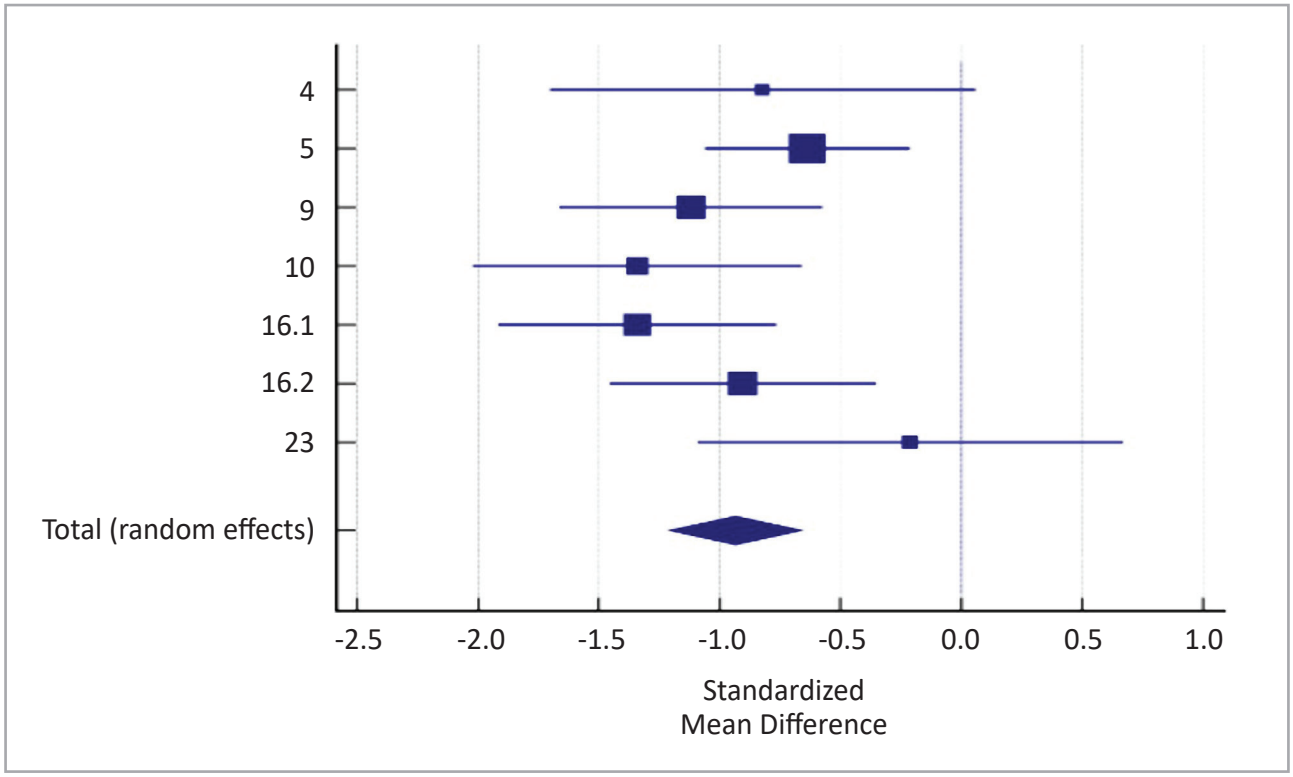

Figure 4: Funnel plot representation of the effects of stem cell therapy on HbA1c in patients with diabetes mellitus using a random-effects model.

decreases in values, with varying degrees of statistical significance.

The meta-analysis revealed substantial heterogeneity, with a Cochran's Q of 84.41 ($p<0.00001$) and an I^2 of 91.71% (Figure 5A). This supports the use of a random-effects model for the subsequent analysis of the data.

Although publication bias calculations were performed using Egger's and Begg's tests (Figure 5B), which indicate the absence of bias, these results cannot be considered conclusive because of the same reasons mentioned previously. On the other hand, from a visual perspective, the asymmetric distribution observed in the forest plot (Figure 5C) indicates a degree of publication bias [13].

Further data analysis demonstrates a trend toward an increase in C-peptide, with a mean of 0.649 (95% CI:

Table 4: Meta-analysis results of the effects of stem cell therapy on HbA1c in patients with diabetes mellitus.

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Random
4	13	10	23	-0.822	0.423	-1.702 to 0.0575			8.73
5	45	46	91	-0.636	0.213	-1.059 to -0.212			21.84
9	31	30	61	-1.120	0.272	-1.665 to -0.575			16.50
10	21	21	42	-1.341	0.336	-2.020 to -0.661			12.40
16.1	29	29	58	-1.341	0.287	-1.916 to -0.765			15.40
16.2	28	29	57	-0.904	0.275	-1.455 to -0.354			16.33
23	11	10	21	-0.212	0.421	-1.092 to 0.669			8.81
Total (random effects)	178	175	353	-0.934	0.139	-1.208 to -0.660	-6.705	<0.001	100.00

Note: Secretory Outcome (C-peptide).

https://doi.org/10.46389/rjd-2026-2155

Table 5: C-peptide values in the studies included in the analysis.

Peptidul C ng/ml									
Study		Year	No cases	Average cases	SD cases	No control	Average control	SD control	Statistic relevance
4	Esteban J. Estrada [8]	2019	13	1.9	1.0	10	0.7	0.4	p=0.0021
5	Li Zang [2]	2022	45	2.07	0.70	46	1.86	0.6	p>0.05
9	Jianxia Hu [16]	2016	31	2.42	0.43	30	1.04	0.33	P<0.01
10	Jinquam Cai [14]	2016	21	0.181	0.091	21	0.091	0.06	p=0.00001
11.1	Jay S Skyler [5]	2015	15	3.892	1.389	16	4.596	2.085	-
11.2	Jay S Skyler [5]	2015	15	3.988	2.00	16	4.596	2.085	-
11.3	Jay S Skyler [5]	2015	15	3.721	1.76	16	4.596	2.085	-
16.1	Zhixian Wu [16]	2024	29	1.7	0.41	29	CDNI	CDNI	
16.2	Zhixian Wu [16]	2024	28	1.6	0.41	29	CDNI	CDNI	
23	Mahmoud Izadi [17]	2022	11	0.31	0.29	10	0.32	0.28	Statistically insignificant

Note: SD – standard deviation; CDNI – study data insufficient to calculate the format of interest.

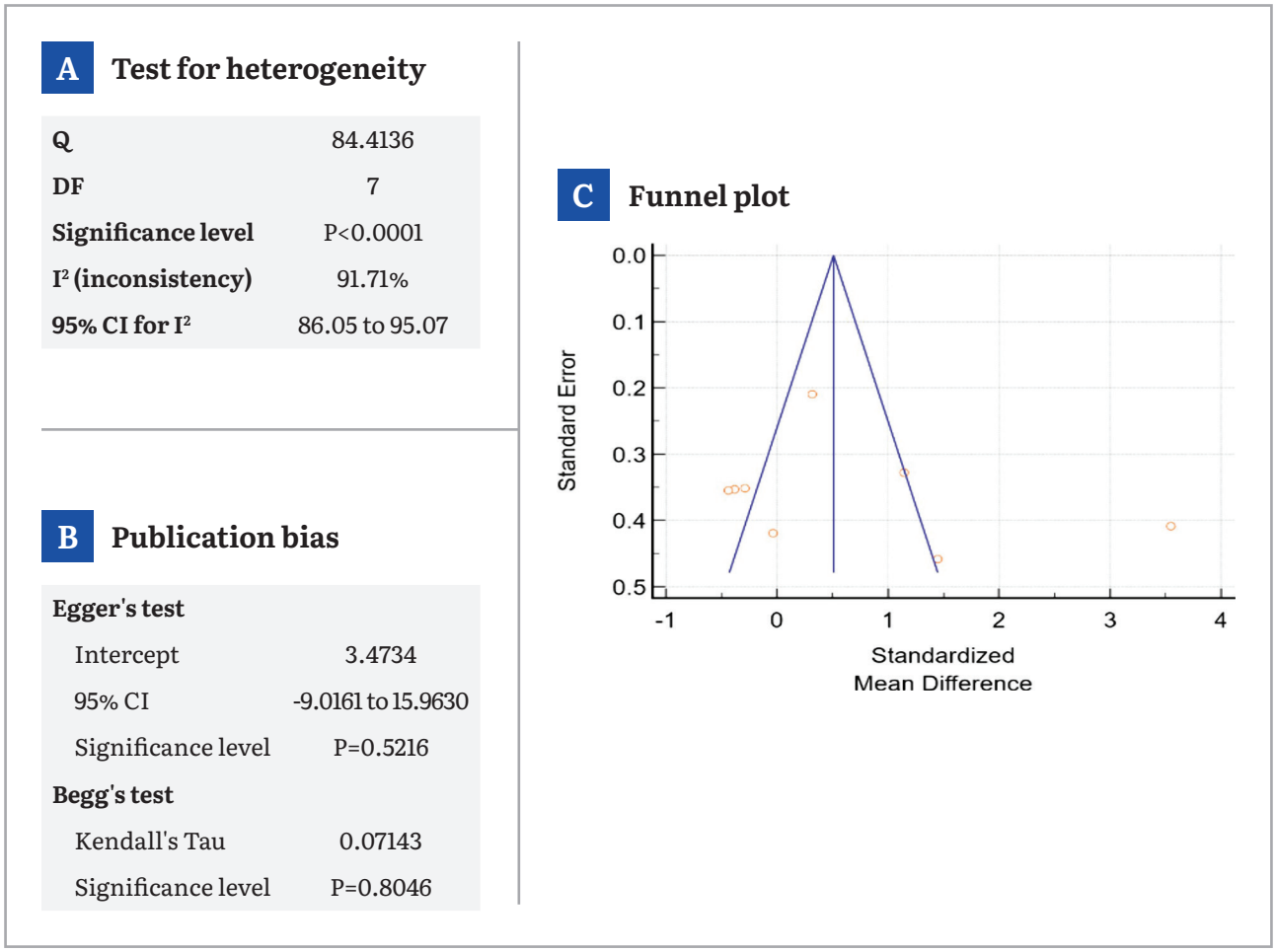

Figure 5: Statistical analysis of study heterogeneity and publication bias for C-peptide (A – Tests for heterogeneity; B – Publication bias; C – Funnel plot).

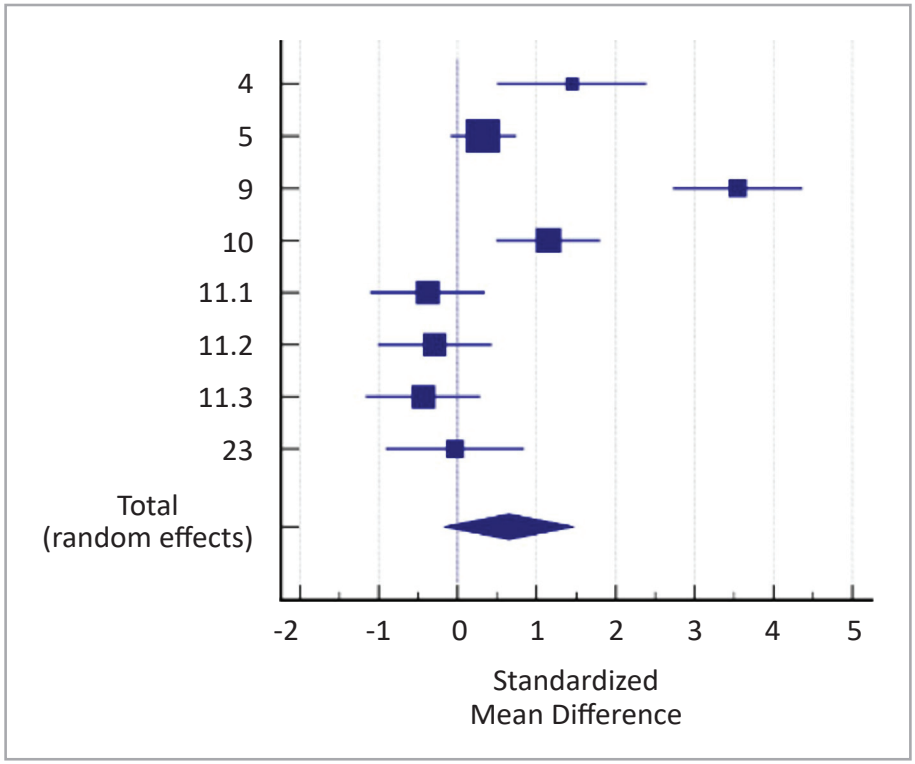

Figure 6: Funnel plot representation of the effects of stem cell therapy on C-peptide in patients with diabetes mellitus using a random-effects model.

−0.179 to 1.476), but this change was not statistically significant (p=0.124) (Figure 6 and Table 6).

Discussion

Diabetes mellitus is a daunting disease characterized by a high degree of clinical heterogeneity, systemic involvement, oxidative stress, and immunosuppression, which can lead to multiple complications, reduced quality of life, and even life-threatening events, continuing to occur despite advances in current therapy [21].

This meta-analysis aimed to evaluate the clinical efficacy of stem cell therapy on metabolic control in patients with diabetes mellitus. We demonstrated that, although the effect on C-peptide does not appear to be statistically significant, stem cell transplantation has a direct effect on lowering HbA1c. The effect size may

Table 6: Meta-analysis results of the effects of stem cell therapy on C-peptide in patients with diabetes mellitus.

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Random
4	13	10	23	1.446	0.458	0.493 to 2.398			11.86
5	45	46	91	0.320	0.209	-0.0961 to 0.735			13.34
9	31	30	61	3.547	0.409	2.729 to 4.365			12.21
10	21	21	42	1.146	0.328	0.484 to 1.808			12.73
11.1	15	16	31	-0.384	0.353	-1.107 to 0.338			12.57
11.2	15	16	31	-0.290	0.352	-1.009 to 0.430			12.58
11.3	15	16	31	-0.440	0.354	-1.165 to 0.285			12.57
23	11	10	21	-0.0336	0.419	-0.912 to 0.844			12.13
Total (random effects)	166	165	331	0.649	0.421	-0.179 to 1.476	1.542	0.124	100.00

https://doi.org/10.46389/rjd-2026-2155

seem modest (0.937, 95% CI: –1.208 to –0.660, p<0.001), but careful interpretation is required due to the clinical importance of the outcome, as well as the baseline and final values of the variable.

As a therapy with a relatively high degree of invasiveness and substantial costs, most existing studies have been conducted on small patient cohorts. The objective of this meta-analysis was to evaluate the effects in as large a group of patients as possible, encompassing both major types of diabetes mellitus prevalent in the population and including a heterogeneous cohort in order to extrapolate the potential applicability of the treatment to the target population. Considering that most current studies are phase I or II clinical trials, the number of patients included in this meta-analysis was satisfactory but insufficient to draw conclusions regarding application in the general population.

The strengths of this meta-analysis are based on the methodological quality of the study search and inclusion process. Nine databases were searched, reducing the likelihood of overlooking relevant studies. The initial establishment of inclusion criteria and the subsequent filtering of studies based on these criteria further strengthen this quality. Where possible, the PRISMA 2020 checklist [22] was applied.

Including both types of diabetes mellitus and not restricting the analysis by the type of stem cells used can be considered a strength, demonstrating that regardless of the patient's pathological substrate or stem cell type, the therapeutic effect can be exerted. However, it can also be seen as a limitation, as no definitive conclusions can be drawn for disease subtypes or for the optimal methodology for applying this treatment.

The limitations of this study arise from the heterogeneity of the included studies, as highlighted by Q and I^2 statistics for both variables, particularly pronounced in the C-peptide analyses. Another limitation involves confounding factors, some of which are difficult or impossible to control. For example, differences in the method of treatment administration cannot be overlooked. Because diabetes is a potentially life-threatening disease, therapy comparisons were made against standard therapy rather than placebo alone. Likewise, patients receiving stem cell therapy also received standard therapy—either oral antidiabetics or insulin—introducing a potential confounder in disease control.

Additional confounders include lifestyle changes or improved compliance due to patient awareness of study participation and close follow-up, particularly relevant for type 2 diabetes. Some studies partially mitigated this by introducing a pre-intervention follow-up period to establish a consistent baseline and reduce variability in HbA1c.

The disease pathophysiology itself is another important confounder. Although *in vitro* conversion of stem cells into insulin-secreting cells has been demonstrated [6, 7], the *in vivo* microenvironment may raise questions about optimal engraftment conditions, including oxidative stress, fluctuating glucose levels, and inflammatory factors, which may impede "homing" and the intended therapeutic effects [21].

Finally, one of the most important limitations is the small number of patients, which currently precludes general clinical application. Nevertheless, the results of this meta-analysis suggest that stem cell therapy is a promising treatment for diabetes mellitus, and further studies with larger and more diverse patient cohorts and varied stem cell types are recommended to determine the optimal cell subtype, whether *in vivo* conversion to insulin-secreting cells occurs, the best administration route, dose, the necessity for repeated dosing or immunosuppressive therapy, and the variation of the therapeutic effect over time.

The study search was limited to results published in one of the scanned databases, in English, up to March 2025. Only scientific articles were considered; conference abstracts or individual reports were excluded, which may have led to the omission of relevant data or publications. Strict inclusion criteria may have excluded studies with questionable methodological quality but still relevant to the topic. The search strategy used general terms, and the lack of alternative terminology may have resulted in missing relevant studies.

A PubMed search using the same terms employed for the current study (diabetes AND stem cell therapy AND glucose levels), filtered for meta-analyses, returned only three results from the last five years. All focused on mesenchymal stem cell therapy for diabetes.

The most relevant to the current study is the meta-analysis by Jingjing He *et al.* [21], published in 2021, which demonstrated results consistent with this study: mesenchymal stem cell therapy resulted in a statistically significant HbA1c reduction of 0.87 (95% CI: –1.53, –0.22; p<0.01), although with higher heterogeneity (I^2=82%). Changes in C-peptide were not statistically significant. In another study focusing exclusively on type 2 diabetes, by Hossein Ranjbaran *et al.* [23] in 2021, a similar trend was reported: a significant HbA1c reduction but a non-significant trend toward increased C-peptide. A more recent study by Umm E. Habiba *et al.* [24], published in 2024, compared the same patient cohorts before and after therapy, demonstrating similar

results: an HbA1c reduction of 0.95 (95% CI: –1.57, –0.33; p=0.003) with a non-significant change in C-peptide.

Conclusions

With the changes in environmental factors and lifestyle, considering the phylogenetic tendency of humans to accumulate energy reserves, it is understandable why diabetes mellitus has become a prominent public health issue in contemporary society. This situation is further exacerbated by advances in available therapies for this condition, which target the outcomes of the pathophysiological process but do not fundamentally alter it, showing limited efficacy in controlling the complications of the disease, which remain the main cause of mortality. The goals of modern medicine are increasingly aligned with the principles of personalized medicine, which, beyond prolonging survival, also emphasize the quality of life achieved through therapy.

This meta-analysis demonstrates that stem cell therapy could provide a significant benefit in the metabolic control of patients with diabetes mellitus and may serve to supplement—or even offer an alternative to—established therapies. However, the current level of knowledge leaves many critical questions unresolved, including the mechanisms of action, duration of therapeutic effect, and which patient populations are most likely to benefit.

Conflict of interest

The author declares no conflicts of interest. The research was conducted under the supervision of Mariana Marginean at "Iuliu Haţieganu" University of Medicine and Pharmacy, with no external influence on the study design or results.

References

1. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 365: 1333–1346, 2005. https://doi.org/10.1016/S0140-6736(05)61032-X
2. Zang L, Li Y, Hao H et al. Efficacy and safety of umbilical cord-derived mesenchymal stem cells in Chinese adults with type 2 diabetes: a single-center, double-blinded, randomized, placebo-controlled phase II trial. Stem Cell Res Ther 13: 180, 2022. https://doi.org/10.1186/s13287-022-02848-6
3. Akil AA, Yassin E, Al-Maraghi A et al. Diagnosis and treatment of type 1 diabetes at the dawn of the personalized medicine era. J Transl Med 19: 137, 2021. https://doi.org/10.1186/s12967-021-02778-6
4. de Klerk E, Hebrok M. Stem cell-based clinical trials for diabetes mellitus. Front Endocrinol (Lausanne) 12: 631463, 2021. https://doi.org/10.3389/fendo.2021.631463
5. Skyler JS, Fonseca VA, Segal KR et al. Allogeneic mesenchymal precursor cells in type 2 diabetes: a randomized, placebo-controlled, dose-escalation safety and tolerability pilot study. Diabetes Care 38: 1742–1749, 2015. https://doi.org/10.2337/dc14-2830
6. Pagliuca FW, Millman JR, Gürtler M et al. Generation of functional human pancreatic β cells in vitro. Cell 159: 428–439, 2014. https://doi.org/10.1016/j.cell.2014.09.040
7. Rezania A, Bruin JE, Arora P et al. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol 32: 1121–1133, 2014. https://doi.org/10.1038/nbt.3033
8. Estrada EJ, Decima JL, Bortman G et al. Combination treatment of autologous bone marrow stem cell transplantation and hyperbaric oxygen therapy for type 2 diabetes mellitus: a randomized controlled trial. Cell Transplant 28: 1632–1640, 2019. https://doi.org/10.1177/0963689719883813
9. National Library of Medicine (US). Using PubMed in evidence-based practice [Internet]. Bethesda (MD): National Library of Medicine. https://www.nlm.nih.gov/oet/ed/pubmed/pubmed_in_ebp/02-100.html
10. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1–12, 1996. https://doi.org/10.1016/0197-2456(95)00134-4
11. Rohatgi A. WebPlotDigitizer [Internet]. Automeris. https://automeris.io
12. MedCalc Statistical Software. Version 23.2.1. Ostend, Belgium: MedCalc Software Ltd, 2024. https://www.medcalc.org
13. Higgins JPT, Thomas J, Chandler J et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4. Cochrane, 2023. https://training.cochrane.org/handbook
14. Cai J, Wu Z, Xu X et al. Umbilical cord mesenchymal stromal cell with autologous bone marrow cell transplantation in established type 1 diabetes: a pilot randomized controlled open-label clinical study. Diabetes Care 39: 149–157, 2016. https://doi.org/10.2337/dc15-0171
15. Wu Z, Huang S, Li S, Cai J, Huang L, Wu W, Chen J, Tan J. Bone marrow mesenchymal stem cell and mononuclear cell combination therapy in patients with type 2 diabetes mellitus: a randomized controlled study with 8-year follow-up. Stem Cell Res Ther. 2024;15(1):339. doi:10.1186/s13287-024-03907-w.
16. Hu J, Wang Y, Gong H et al. Long-term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes. Exp Ther Med 12: 1857–1866, 2016. https://doi.org/10.3892/etm.2016.3544
17. Izadi M, Sadr Hashemi Nejad A, Moazenchi M et al. Mesenchymal stem cell transplantation in newly diagnosed type 1 diabetes patients: a phase I/II randomized placebo-controlled clinical trial. Stem Cell Res Ther 13: 264, 2022. https://doi.org/10.1186/s13287-022-02941-w
18. Sterne JAC, Savović J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366: l4898, 2019. https://doi.org/10.1136/bmj.l4898
19. Pohanka M. Glycated hemoglobin and methods for its point-of-care testing. Biosensors 11: 70, 2021. https://doi.org/10.3390/bios11030070

 https://doi.org/10.46389/rjd-2026-2155

20. Hoekstra JB, van Rijn HJ, Erkelens DW et al. C-peptide. Diabetes Care 5: 438–446, 1982. https://doi.org/10.2337/diacare.5.4.438
21. He J, Kong D, Yang Z et al. Clinical efficacy on glycemic control and safety of mesenchymal stem cells in patients with diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. PLoS One 16: e0247662, 2021. https://doi.org/10.1371/journal.pone.0247662
22. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372: n71, 2021. https://doi.org/10.1136/bmj.n71
23. Ranjbaran H, Mohammadi Jobani B, Amirfakhrian E et al. Efficacy of mesenchymal stem cell therapy on glucose levels in type 2 diabetes mellitus: a systematic review and meta-analysis. J Diabetes Investig 12: 803–810, 2021. https://doi.org/10.1111/jdi.13404
24. Habiba UE, Khan N, Greene DL et al. Meta-analysis shows that mesenchymal stem cell therapy can be a possible treatment for diabetes. Front Endocrinol (Lausanne) 15: 1380443, 2024. https://doi.org/10.3389/fendo.2024.1380443