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META-ANALYSIS

Autologous and allogeneic mesenchymal stem cell-based therapies for diabetes mellitus: A systematic review and meta-analysis

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Abstract

BACKGROUND

Diabetes mellitus (DM) is a global health concern, characterized by insulin resistance and β-cell dysfunction. Traditional treatments often fail to address underlying mechanisms, necessitating alternative therapies. Mesenchymal stem cell (MSC)-based therapies have shown promise due to their regenerative and immunomodulatory properties. However, evidence on their efficacy and safety in type 2 DM remains limited and further evaluation is needed.

AIM

To evaluate the safety, efficacy and therapeutic potential of MSC-based therapies in type 2 DM.

METHODS

This systematic review analyzed studies published between 2000 and 2025, focusing on autologous and allogeneic MSC therapies in DM. Studies were identi-

fied from various databases, including clinical and preclinical trials. Outcomes related to glycemic control, insulin requirements, β-cell function, and safety were assessed.

RESULTS

MSC-based therapies significantly improved glycemic control, reduced insulin requirements and enhanced β-cell function in both clinical and preclinical settings. Safety profiles were favorable, with minimal adverse effects observed, primarily transient and self-limiting. No fatal events were reported. Variability in treatment outcomes and the need for standardized protocols were challenges.

CONCLUSION

MSC-based therapies offer a promising alternative to conventional DM treatments, significantly improving glycemic control and safety. Further research is needed to refine protocols and confirm long-term efficacy.

Key Words: Type 2 diabetes mellitus; Metabolic disorders; Obesity; Insulin lessen; Insulin resistance; Cell therapy; Mesenchymal stem cell

Core Tip: This comprehensive review explores the potential of mesenchymal stem cell (MSC)-based therapies, both autologous and allogeneic, for treating type 2 diabetes mellitus. The study evaluates the safety, efficacy, and therapeutic benefits of MSCs, highlighting improvements in glycemic control, reductions in insulin requirements and enhanced β-cell function. While MSC-based therapies show promising results with minimal adverse effects, challenges remain in standardizing treatment protocols. Future research should aim to refine these therapies and assess their long-term effects through large-scale clinical trials.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by elevated blood glucose levels due to insulin insufficiency, either from defects in insulin secretion or action. It is a global health concern, with over 420 million people affected in 2021, and projections show a rise to 578 million by 2030[1,2]. Type 2 DM (T2DM), accounting for over 90% of cases, is primarily driven by insulin resistance and β-cell dysfunction. The global prevalence of T2DM exhibits disparities, with urban populations and high-income nations being more affected than rural areas and low-income countries[3]. T2DM management focuses on lifestyle modifications, such as diet and physical activity, and requires a multifaceted therapeutic approach, as insulin resistance persists while insulin secretion deficits increase over time. While insulin remains central to treatment, other therapies targeting insulin resistance and β-cell protection are essential[4,5].

Recent advances include using amylin analogs, glucagon-like peptides, and sodium-glucose co-transporter inhibitors, potentially benefiting glycemic control and kidney function[6,7]. Weight management is critical, especially considering the link between T2DM and obesity. Recent increases in diabetes-related mortality highlight the need for innovative treatments. Mesenchymal stem cell (MSC) therapy has emerged as a promising option, potentially addressing key aspects of T2DM pathogenesis, such as insulin resistance and β-cell protection. This study explores the potential of MSC therapy in T2DM management, shedding light on its prospects.

MATERIALS AND METHODS

Research question

The primary objective of this systematic review was to investigate how autologous and allogeneic transplanted MSC-based therapies are used for DM treatment. The protocol for this meta-analysis was registered in the International Prospective Register of Systematic Reviews PROSPERO, registry ID: CRD42023486358.

Search strategy and selection criteria

In this study, we adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews[8]. An exhaustive search was conducted in the PubMed, Scopus, and Web of Science databases until January 2025, encompassing all primary studies that examined the relationship between MSC-based therapies for DM. The search strategy

involved the keywords: "mesenchymal stem cell" AND "Diabetes Mellitus". We used logical operators "OR" and "AND" to separate terms within each set and combine the sets, respectively (Supplementary Table 1). Additionally, we manually examined the citation indices of relevant studies and reviewed articles from the initial search. There were no chronological restrictions and the search continued up to the present date.

Inclusion criteria

To be included in this systematic review, studies had to meet the following requirements: (1) Inclusion of observational studies, including prospective and retrospective cohort studies, case-control designs, and crossover studies; (2) Assessment of MSC as a therapeutic factor; (3) Enrolled participants were human and animal models; and (4) The primary outcome focused on changes in DM.

Exclusion criteria

Exclusion criteria for this systematic review encompassed the following categories: (1) *In vitro* studies; (2) Secondary review articles or derivative research; and (3) Case reports, editorials, abstracts, unpublished studies, and manual papers.

Study selection

Following predefined inclusion and exclusion criteria, two authors (Zare A and Tamadon A) screened relevant literature in the PubMed, Scopus, and Web of Science databases. Initial screening involved reviewing titles and abstracts, followed by a comprehensive examination of the full texts of selected articles. Any discrepancies were resolved through discussion between the two mentioned authors. Furthermore, the researchers manually searched reference lists associated with relevant studies. In cases where an article not previously identified by the reviewers was deemed potentially suitable for inclusion, a virtual conference took place between Zare A and Tamadon A. The discussion concerned whether the recommended article aligned with the established inclusion and exclusion criteria.

Assessment of risk of bias

Potential publication biases or selective reporting within the randomized controlled trial (RCT) studies were examined by reviewing the study registration protocols and analyzing the timelines of both the study execution and publication. Additionally, we investigated whether recent studies with larger sample sizes and more favorable outcomes disproportionately impacted the meta-analysis results. When reporting bias was identified, all pertinent data from these studies were documented, even if they could not be included in the meta-analysis. The conclusions drawn from RCTs were retained in their original form as provided by the authors.

The risk of bias across studies was evaluated following the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions, using Review Manager 5.1 (Cochrane Collaboration, United Kingdom)[9]. This evaluation included seven key domains: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential biases. The GRADE approach assessed the evidence's certainty[10].

Moreover, we conducted a risk-of-bias assessment of the retrospective cohort study using the ROBINS-I framework for non-randomized studies of interventions. Two reviewers (Zare A and Tamadon A) independently evaluated each study outcome against ROBINS-I's seven bias domains: (1) Bias due to confounding; (2) Bias in selection of participants into the study; (3) Bias in classification of interventions; (4) Bias due to deviations from intended interventions; (5) Bias due to missing data; (6) Bias in measurement of outcomes; and (7) Bias in selection of the reported result - following the guidance and signaling questions outlined by Sterne *et al*[11] in 2016. Discrepancies were resolved by consensus discussion, and judgments for each domain were recorded on a four-level scale (low, moderate, severe, critical). The overall risk-of-bias judgment for each outcome was then derived by taking the highest level of risk identified across the domains. Key study characteristics - including the small sample size (n = 28), retrospective design, baseline imbalances, and absence of a prospectively registered analysis plan - were extracted from the published report to inform domain-specific ratings.

Statistical analysis

We employed a random effects model for the meta-analysis based on the heterogeneity observed across the studies. Significant variability in the study outcomes determined the choice of a random effects model, which indicated that the studies were not sufficiently homogeneous to justify a fixed effects model. We used mean ± SD for statistical analysis, as these are appropriate for summarizing continuous outcomes such as hemoglobin A1c (HbA1c) and insulin requirements. This approach allows for the pooling of results while accounting for the variation in study populations. The random effects model was chosen because it appropriately handles the variation in effect sizes across studies and provides more generalized estimates of the overall effect.

Summary measures

The principal summary measures used in this meta-analysis include the difference in means for continuous variables such as HbA1c, fasting blood glucose (FBG), C-peptide levels and insulin requirements. Statistical significance was evaluated using P values for each comparison. Additionally, effect sizes were estimated and outcomes were pooled using a random effects model to account for the heterogeneity across the studies.

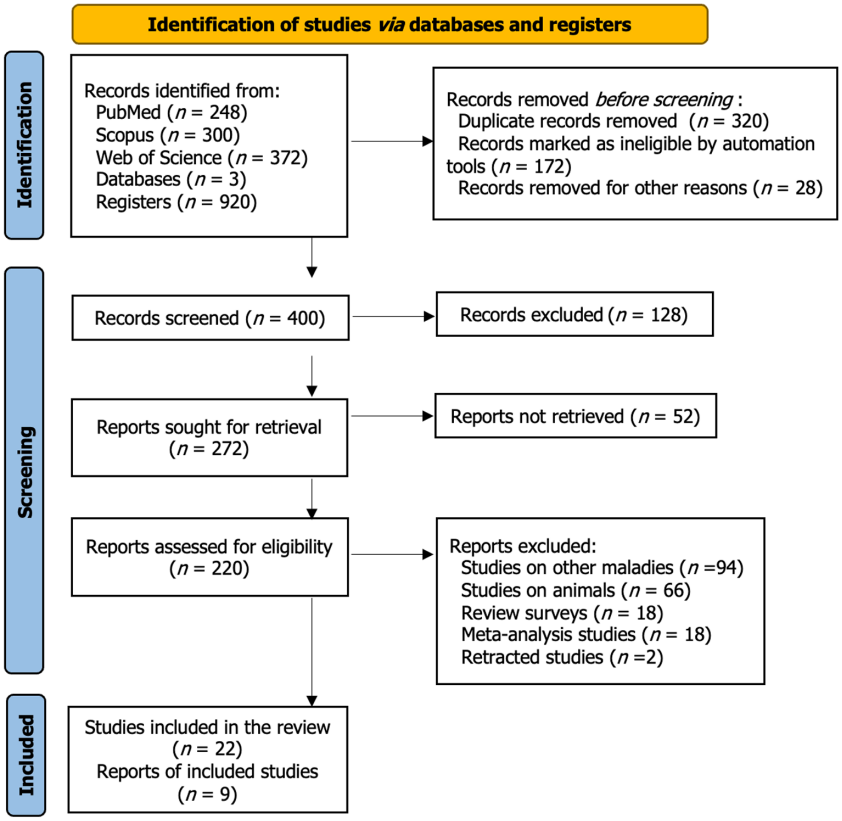


Figure 1 Preferred Reporting Items for Systematic Reviews - a flow chart of the study selection process for the effects of mesenchymal stem cell-based therapies for diabetes mellitus.

Synthesis of results

Data were pooled using a random effects model due to significant heterogeneity observed among the included studies. The I^2 statistic was used to assess the consistency of results across studies. Results were summarized for key glycemic outcomes including HbA1c, FBG, C-peptide levels, and insulin requirements. For each meta-analysis, I^2 values were calculated to determine the degree of variation between study outcomes and significance was tested using P values for each outcome. This approach allowed for a comprehensive evaluation of the effects of MSC-based therapies across different types of studies.

RESULTS

Selected studies

Following keyword formulation, we engaged with the PubMed, Scopus, and Web of Science databases and observed the thematic organization of data within distinct categories. Figure 1 depicts a schematic representation detailing the progression of the study's article selection procedure. Initially, from January 1, 2025, a pool of prospective articles (920 studies) was identified in PubMed (248 studies), Scopus (300 studies), and Web of Science databases (372 studies). Subsequently, some of the articles were eliminated on the grounds of incongruence with the designated article type. From this pool, English-speaking papers were taken into account to make a systematic review, the data of which can be checked by the primary sources. Papers that did not encompass quantified assessments of impact or outcomes were excluded as a culmination of this winnowing process, a compilation of 22 studies satisfying the predefined criteria for inclusion in the analysis by systematic review. Among these 22 studies, nine were selected for meta-analysis and constituted the ultimate sample.

Study characteristics

The cohort encompassed within this systematic review comprised 22 papers focused on the characteristics of the specific issue related to DM features or discussed basic principles. Twenty-two investigations were of longitudinal design, 21 adopted a prospective approach and 13 employed a randomized controlled design. The essential attributes of the chosen articles are delineated in Supplementary Table 2. Furthermore, Supplementary Table 3 lists detailed features of participants in the studies in which the effects of MSC-based therapies for DM are observed. Only one of these 22 studies is single-gender. Besides, China has the most significant number of studies in which the effects of MSC-based therapies for DM are examined, with 10 studies. Moreover, some studies are single-arm and have no control group. Other details

are demonstrated in Supplementary Table 3.

Studies that are chosen for assessing eligibility for meta-analysis

Twenty-two studies were selected to evaluate the eligibility for undergoing the meta-analysis. Nine studies were selected for meta-analysis among 22 that examined the different impacts of MSC-based therapies on DM. Table 1 displays various features of these 22 studies and the glycemic outcomes they examine[12-33].

Table 1 Glycemic outcomes in each of the studies that are chosen for assessing eligibility for meta-analysis

Ref.	Type of study							HbA1c	FBG	C-peptide levels	PBG	Insulin requirements
	Randomized	Non-randomized	Blindness	Prospective	Retrospective	Parallel	Cross over					
Cai *et al* [12][1]	+		NB	+		+		+	+	+		+
Packham *et al*[13][1]	+		DB	+		+		+				
Carlsson *et al*[14][1]	+		NB	+		+		+		+		+
Leão *et al*[15][1]		+	NB		+	+		+				
Skyler *et al*[16][1]	+		SB	+		+			+	+		
Thakkar *et al*[17][1]		+	NB	+		+		+	+	+	+	+
Zhao *et al*[18][1]	+		NB	+		+		+		+		
Wu *et al* [19][1]	+		NB	+		+		+	+	+		+
Wu *et al* [20][1]	+		NB	+		+		+	+	+		+
Vanikar *et al*[21][2]		+	NB	+		+		+	+	+	+	+
Bhansali *et al*[22][2]	+		SB	+		+		+	+	+		+
Hu *et al* [23][2]	+		SB	+		+		+	+	+		+
Hu *et al* [24][2]	+		DB	+		+		+	+	+	+	+
Jiang *et al*[25][2]		+	NB	+				+	+	+		+
Li *et al* [26][2]		+	NB	+				+	+	+	+	+
Lian *et al* [27][2]		+	NB	+				+	+	+	+	+
Liu *et al* [28][2]		+	NB	+		+		+	+	+	+	+
Moon *et al*[29][2]	+		SB	+		+		+	+		+	
Nguyen *et al*[30][2]	+		NB	+		+		+	+	+		+
De Guzman *et al*[31][2]		+	NB	+				+	+			+
Guan *et al*[32][2]		+	NB	+				+	+	+		
Purwati		+	NB	+				+	+	+		+

et al[33][2]				

[1]Studies that have undergone meta-analysis.
[2]Studies that have not undergone meta-analysis.
HbA1c: Hemoglobin A1c; FBG: Fasting blood glucose; PBG: Postprandial blood glucose; DB: Double blind; NB: Not blinded; SB: Single blinded.

The characteristics of MSCs that are used in studies that underwent meta-analysis

Based on the present study, among all studies that underwent meta-analysis, five studies have used allogeneic MSCs, and four studies have utilized autologous types of the mentioned cells (Table 2). Moreover, bone marrow has been the most interesting source for achieving MSCs among other MSC sources (Table 2). Furthermore, the pancreas was the main target for MCS transplantation, among other human organs (Table 2). Additionally, more information about MSCs used in studies that underwent meta-analysis and the various methods by which MSCs are grafted are mentioned in Table 2.

Table 2 Detailed information about the characteristics of mesenchymal stem cells that are used in studies that underwent meta-analysis, and the various methods by which mesenchymal stem cells are grafted

Ref.	Source of MSCs	Type of graft of MSCs	Type of grafting method of MSCs	Targeted tissue/organ
Cai *et al*[12]	UC-MSCs and aBM-MNCs	Allogeneic	Intra-arterial infusion *via* supra-selective pancreatic artery cannulation	Pancreas
Packham *et al*[13]	BM-MPCs	Allogeneic	IV infusion	Kidneys
Carlsson *et al*[14]	BM-MSCs	Autologous	IV infusion	Pancreas
Leão *et al*[15]	ASCs	Allogeneic	IV infusion	Systemic administration
Skyler *et al*[16]	BM-MPCs	Allogeneic	IV infusion	Systemic administration
Thakkar *et al*[17]	IS-AD-MSCs and BM-HSCs	Autologous	Infusion into the portal vein, thymic circulation, and subcutaneous tissue	Pancreas and subcutaneous tissue
Zhao *et al*[18]	CB-SCs	Allogeneic	Stem cell educator therapy Re-infusion of educated lymphocytes into the patient's circulation	Pancreas
Wu *et al*[19]	BM-MNCs	Autologous	Pancreatic intra-arterial infusion *via* the dorsal pancreatic artery	Pancreas
Wu *et al*[20]	BM-MSCs	Autologous	Intra-arterial and intravenous infusion	Pancreas

MSC: Mesenchymal stem cell; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; aBM-MNCs: Autologous bone marrow mononuclear cells; BM-MPCs: Bone marrow-derived mesenchymal progenitor cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; ASCs: Adipose-derived mesenchymal stem cells; BM-MPCs: Bone marrow-derived mesenchymal progenitor cells; IV: Intravenous; IS-AD-MSCs: Adipose tissue derived insulin-secreting mesenchymal stem cells; BM-HSCs: Bone marrow-derived hematopoietic stem cells; CB-SCs: Cord-blood-derived multipotent stem cells; BM-MNCs: Bone marrow mononuclear cells.

Studies that are not chosen for meta-analysis

In our research, 13 studies were not included in the meta-analysis. However, these 13 studies demonstrated the favorable effects of MSC-based therapies in treating DM (Table 2). Table 2 depicts the information about the glycemic impacts of the mentioned cells on DM in detail. Moreover, among these 13 studies, five were RCTs that did not contain enough data to undergo meta-analysis. The data about these five studies is depicted in Supplementary Table 4.

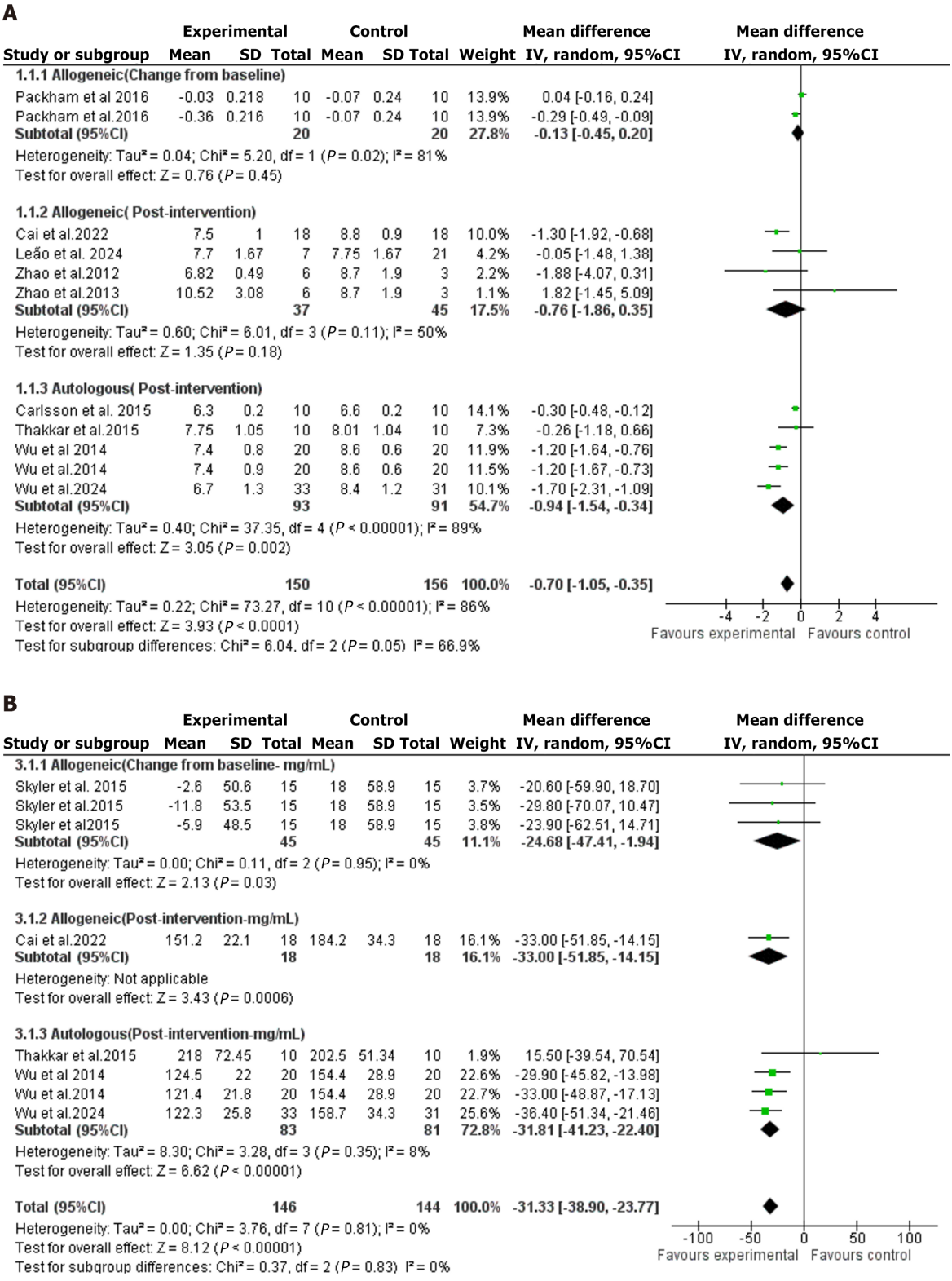
The results of the effect of MSCs on DM

Based on the information in Supplementary Table 2, MSCs can affect various glycemic outcomes in patients suffering from DM, including improved glycemic control, increased insulin sensitivity, reduced insulin requirements, improved β-cell function and reduced diabetes-related complications. Besides, sustained glycemic control and maintenance of β-cell function over time are long-term effects of MSCs on patients suffering from DM (Supplementary Table 2). Furthermore, Supplementary Table 5 demonstrates that MSCs can potentially ameliorate the condition of patients with DM by reducing HbA1C, FBG, postprandial blood glucose and insulin requirements. MSC therapy positively affects various glycemic outcomes in patients with DM, especially in improving glycemic control, enhancing insulin secretion (evidenced by increased C-peptide levels) and reducing insulin dependency. However, the long-term effects can vary with some fluctu-

ations (*e.g.*, return to baseline HbA1c) (Supplementary Table 5). Supplementary Tables 2 and 5 also provide detailed information about various types of MSCs and their impacts on DM.

The results of the meta-analysis for analyzing the effects of bone marrow-derived MSCs on DM

The results of the meta-analysis performed in this manuscript have demonstrated that bone marrow-derived MSCs can decrease HbA1C (P = 0.0005), FBG (P < 0.00001), and insulin requirements (P = 0.03), as well as a slight increase in C-peptide levels (P = 0.03) in patients with DM (Figure 2).



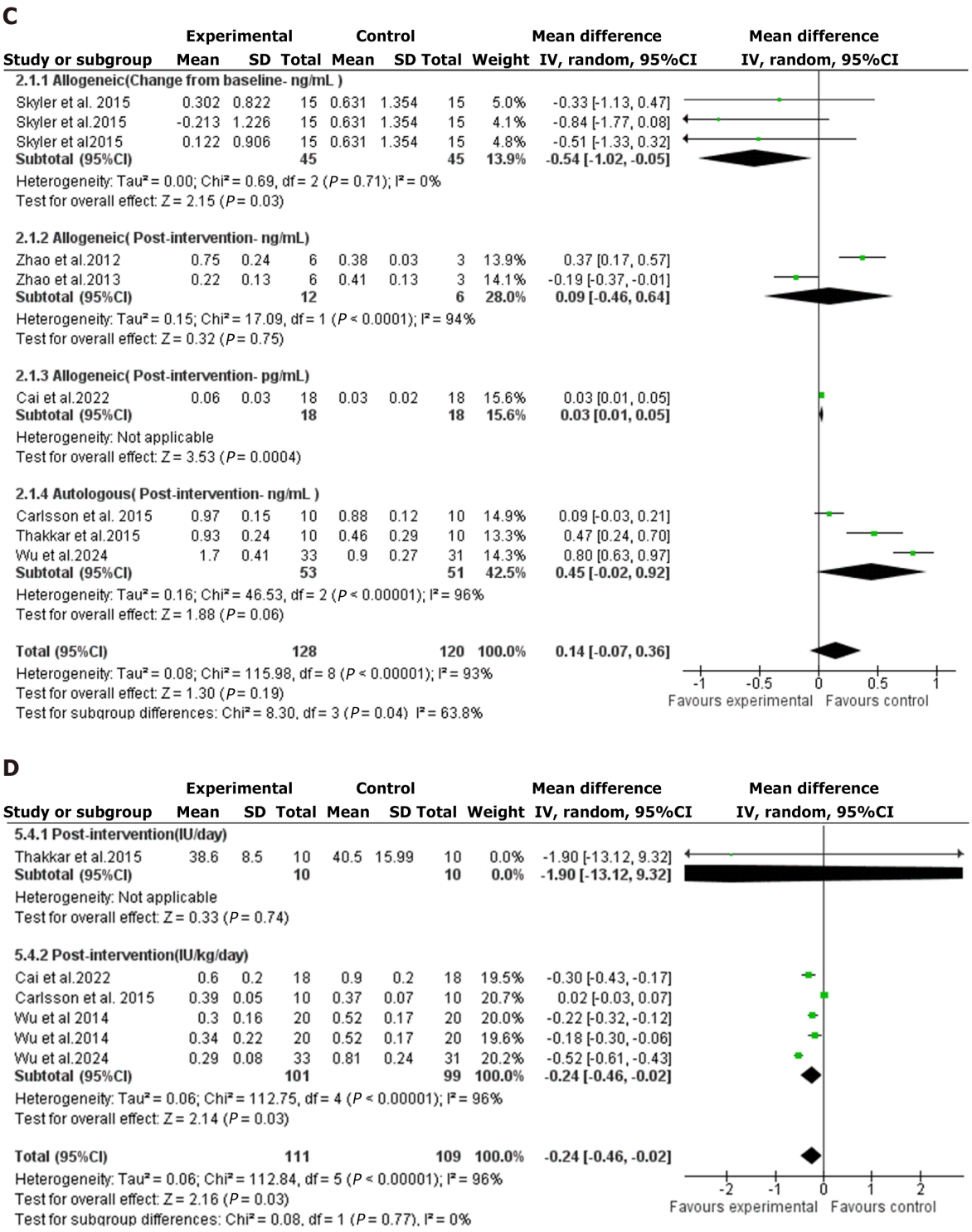


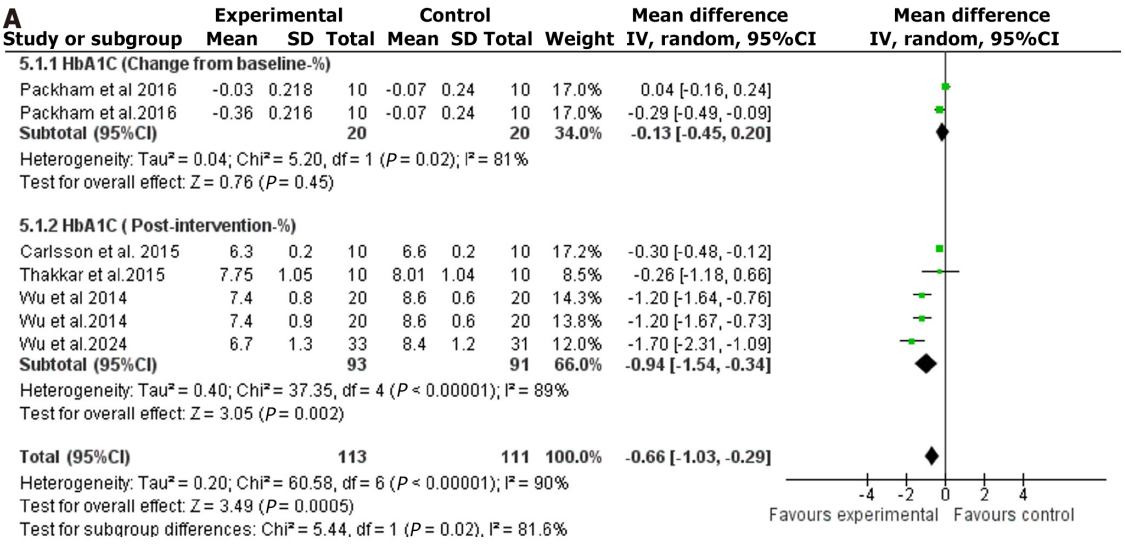
Figure 2 The forest plots resulted from the meta-analysis of the effect of bone marrow-derived mesenchymal stem cell-based therapies on various glycemic outcomes. A: Hemoglobin A1c; B: Fasting blood glucose; C: C-peptide level; D: Insulin requirements. CI: Confidence interval.

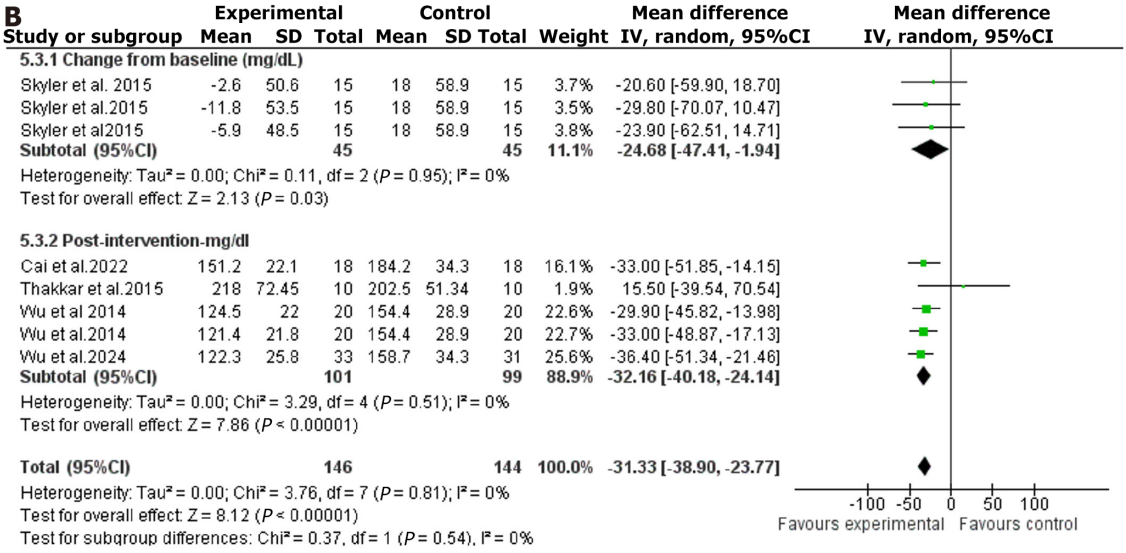
The results of the meta-analysis for analyzing the effects of allogenic and autologous transplanted MSCs on DM

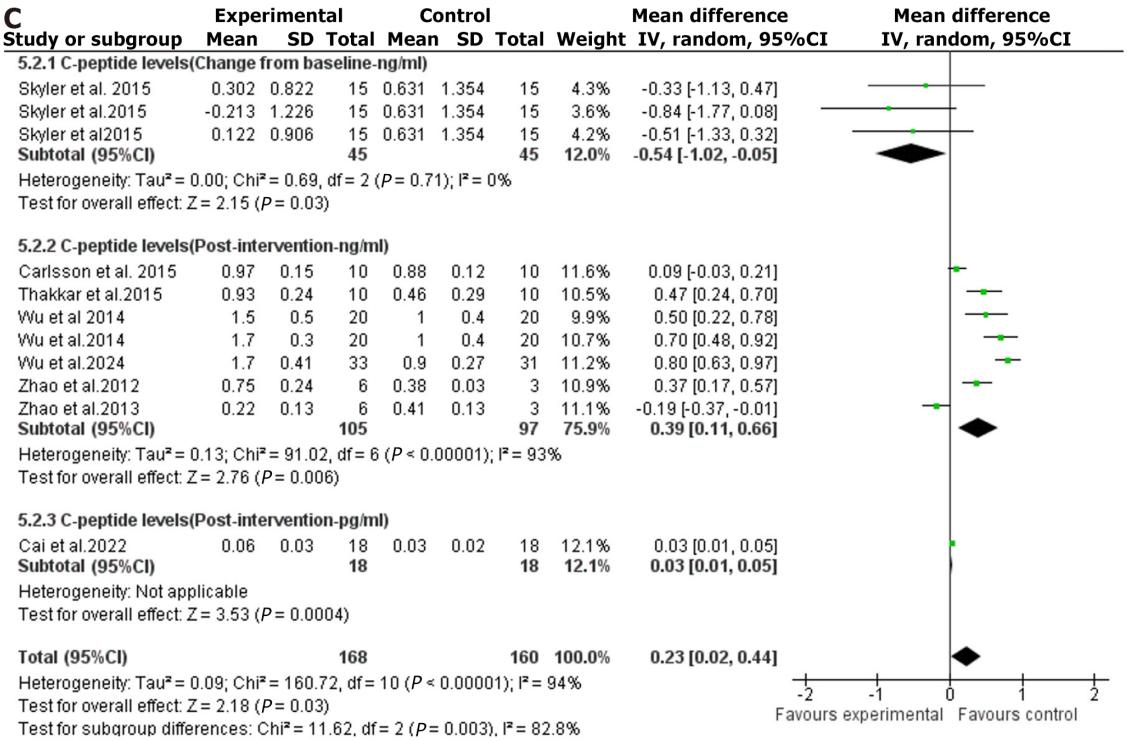
Figure 3 displays that allogeneic transplanted MSCs cannot affect HbA1c, and C-peptide levels can decrease FBG (P values are 0.03 and 0.0006) and insulin requirements ($P < 0.00001$). On the other hand, autologous transplanted MSCs can decrease HbA1c ($P = 0.002$), FBG ($P < 0.00001$) and insulin requirements ($P < 0.00001$). Notably, these MSCs cannot impact the C-peptide level (Figure 3). Our meta-analysis showed that MSC-based therapies can reduce HbA1C, FBG and insulin requirements. However, they cannot affect the level of C-peptide in patients with DM (Figures 2 and 3).

Assessment of the risk of bias of the studies that have undergone meta-analysis

The risk of bias in studies that are selected for meta-analysis is demonstrated in Figure 4. For the study performed by Leão *et al*[15], our ROBINS-I assessment found a moderate overall risk of bias. Confounding was moderate - patients


A
Experimental
Control
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
5.1.1 HbA1C (Change from baseline-%)
Packham et al 2016 -0.03 0.218 10 -0.07 0.24 10 17.0% 0.04 [-0.16, 0.24]
Packham et al.2016 -0.36 0.216 10 -0.07 0.24 10 17.0% -0.29 [-0.49, -0.09]
Subtotal (95%CI) 20 20 34.0% -0.13 [-0.45, 0.20]
Heterogeneity: Tau² = 0.04; Chi² = 5.20, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.76 (P = 0.45)
5.1.2 HbA1C (Post-intervention-%)
Carlsson et al. 2015 6.3 0.2 10 6.6 0.2 10 17.2% -0.30 [-0.48, -0.12]
Thakkar et al.2015 7.75 1.05 10 8.01 1.04 10 8.5% -0.26 [-1.18, 0.66]
Wu et al 2014 7.4 0.8 20 8.6 0.6 20 14.3% -1.20 [-1.64, -0.76]
Wu et al.2014 7.4 0.9 20 8.6 0.6 20 13.8% -1.20 [-1.67, -0.73]
Wu et al.2024 6.7 1.3 33 8.4 1.2 31 12.0% -1.70 [-2.31, -1.09]
Subtotal (95%CI) 93 91 66.0% -0.94 [-1.54, -0.34]
Heterogeneity: Tau² = 0.40; Chi² = 37.35, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.05 (P = 0.002)
Total (95%CI) 113 111 100.0% -0.66 [-1.03, -0.29]
Heterogeneity: Tau² = 0.20; Chi² = 60.58, df = 6 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.49 (P = 0.0005)
Test for subgroup differences: Chi² = 5.44, df = 1 (P = 0.02), I² = 81.6%
-4 -2 0 2 4
Favours experimental Favours control


B
Experimental
Control
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
5.3.1 Change from baseline (mg/dL)
Skyler et al. 2015 -2.6 50.6 15 18 58.9 15 3.7% -20.60 [-59.90, 18.70]
Skyler et al.2015 -11.8 53.5 15 18 58.9 15 3.5% -29.80 [-70.07, 10.47]
Skyler et al2015 -5.9 48.5 15 18 58.9 15 3.8% -23.90 [-62.51, 14.71]
Subtotal (95%CI) 45 45 11.1% -24.68 [-47.41, -1.94]
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)
5.3.2 Post-intervention-mg/dl
Cai et al.2022 151.2 22.1 18 184.2 34.3 18 16.1% -33.00 [-51.85, -14.15]
Thakkar et al.2015 218 72.45 10 202.5 51.34 10 1.9% 15.50 [-39.54, 70.54]
Wu et al 2014 124.5 22 20 154.4 28.9 20 22.6% -29.90 [-45.82, -13.98]
Wu et al.2014 121.4 21.8 20 154.4 28.9 20 22.7% -33.00 [-48.87, -17.13]
Wu et al.2024 122.3 25.8 33 158.7 34.3 31 25.6% -36.40 [-51.34, -21.46]
Subtotal (95%CI) 101 99 88.9% -32.16 [-40.18, -24.14]
Heterogeneity: Tau² = 0.00; Chi² = 3.29, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 7.86 (P < 0.00001)
Total (95%CI) 146 144 100.0% -31.33 [-38.90, -23.77]
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 7 (P = 0.81); I² = 0%
Test for overall effect: Z = 8.12 (P < 0.00001)
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² = 0%
-100 -50 0 50 100
Favours experimental Favours control


C
Experimental
Control
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
5.2.1 C-peptide levels(Change from baseline-ng/ml)
Skyler et al. 2015 0.302 0.822 15 0.631 1.354 15 4.3% -0.33 [-1.13, 0.47]
Skyler et al.2015 -0.213 1.226 15 0.631 1.354 15 3.6% -0.84 [-1.77, 0.08]
Skyler et al2015 0.122 0.906 15 0.631 1.354 15 4.2% -0.51 [-1.33, 0.32]
Subtotal (95%CI) 45 45 12.0% -0.54 [-1.02, -0.05]
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)
5.2.2 C-peptide levels(Post-intervention-ng/ml)
Carlsson et al. 2015 0.97 0.15 10 0.88 0.12 10 11.6% 0.09 [-0.03, 0.21]
Thakkar et al.2015 0.93 0.24 10 0.46 0.29 10 10.5% 0.47 [0.24, 0.70]
Wu et al 2014 1.5 0.5 20 1 0.4 20 9.9% 0.50 [0.22, 0.78]
Wu et al.2014 1.7 0.3 20 1 0.4 20 10.7% 0.70 [0.48, 0.92]
Wu et al.2024 1.7 0.41 33 0.9 0.27 31 11.2% 0.80 [0.63, 0.97]
Zhao et al.2012 0.75 0.24 6 0.38 0.03 3 10.9% 0.37 [0.17, 0.57]
Zhao et al.2013 0.22 0.13 6 0.41 0.13 3 11.1% -0.19 [-0.37, -0.01]
Subtotal (95%CI) 105 97 75.9% 0.39 [0.11, 0.66]
Heterogeneity: Tau² = 0.13; Chi² = 91.02, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.76 (P = 0.006)
5.2.3 C-peptide levels(Post-intervention-pg/ml)
Cai et al.2022 0.06 0.03 18 0.03 0.02 18 12.1% 0.03 [0.01, 0.05]
Subtotal (95%CI) 18 18 12.1% 0.03 [0.01, 0.05]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.53 (P = 0.0004)
Total (95%CI) 168 160 100.0% 0.23 [0.02, 0.44]
Heterogeneity: Tau² = 0.09; Chi² = 160.72, df = 10 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Chi² = 11.62, df = 2 (P = 0.003), I² = 82.8%
-2 -1 0 1 2
Favours experimental Favours control

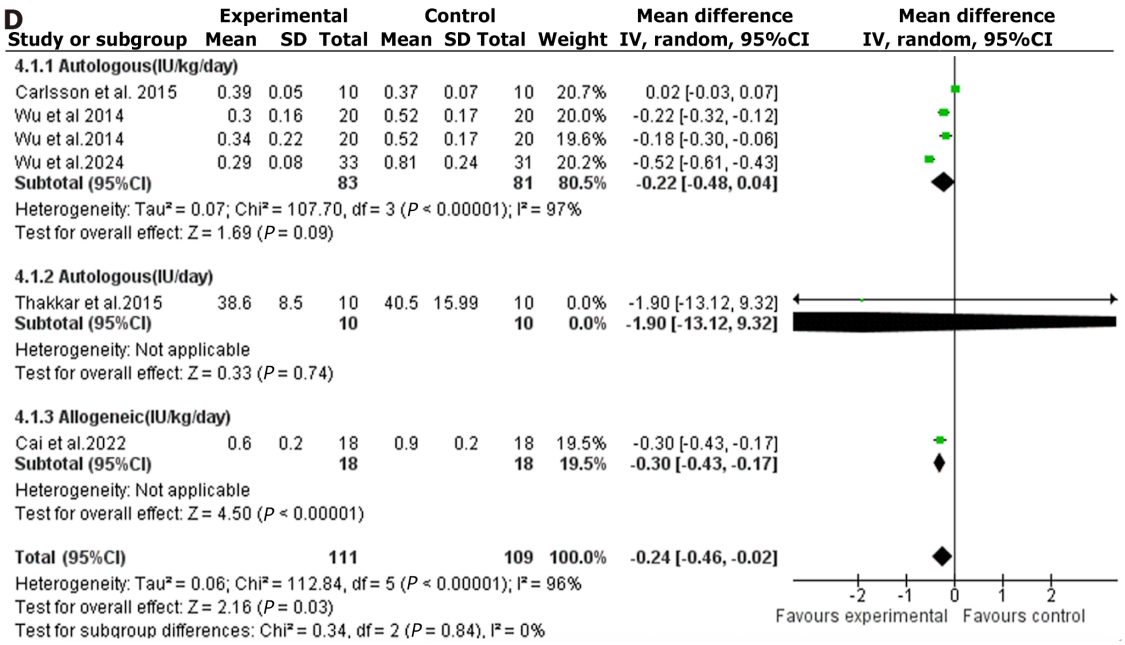


Figure 3 The forest plots resulted from the meta-analysis of the effect of allogeneic and autologous transplanted mesenchymal stem cell-based therapies on various glycemic outcomes. A: Hemoglobin A1c; B: Fasting blood glucose; C: C-peptide level; D: Insulin requirements. CI: Confidence interval; HbA1c: Hemoglobin A1c.

receiving stem-cell plus vitamin D were older and had higher body mass index - while selection bias was moderate due to the single-center, retrospective design. All other domains were low risk except selective reporting, which was moderate given the lack of a registered protocol. Moreover, Supplementary Table 6 provides detailed information about the reasons for the high risk of bias in studies that have undergone meta-analysis.

Assessment of safety and adverse side effects of studies in which the effects of MSC-based therapies on DM have been examined

The present study demonstrated that therapeutic approaches based on MSCs have no serious side effects, and the adverse effects of these kinds of curative approaches are temporary and occur in a minority of participants (Supplementary Table 7). Moreover, Supplementary Table 7 depicts different side effects that occurred in stem cell-based therapies in patients with DM. Additionally, the present study demonstrated no fatal impact of the mentioned therapies that have been reported until today (Supplementary Table 7). Therefore, based on the findings noted in Supplementary Table 7, Figure 5 depicts the safety assessment of MSC-based therapies for DM.

DISCUSSION

The effects of MSC-based therapies on patients with DM

In recent years, various studies have tried to elucidate different impacts of MSC-based therapies on DM[34]. Interestingly, these studies have represented the favorable effects of the mentioned therapies on patients suffering from DM[35]. For instance, in one study, MSC-based therapeutic approaches have had different positive influences on the condition of DM, including improving glycemic control by reducing HbA1C levels and decreasing fasting blood glucose levels, enhancing β-cell functions by increasing fasting C-peptide levels, reducing dependence on medication through lowering insulin dosage and diminishing the requirement for oral hyperglycemic drugs[36]. Moreover, the present study has also demonstrated that the use of MSC-based therapies in DM can lead to some favorable effects, such as reducing FBG and HbA1c levels, reducing the need for insulin, as well as increasing the level of C-peptide in the patients suffering from DM (Table 2 and Supplementary Table 2). These results align with previous studies' results and confirm the positive influences of MSC-based therapeutic approaches for treating DM.

Other effects of MSC-based therapies on patients with DM

Based on the information in Supplementary Table 2, MSC-based therapies demonstrated some other impacts on patients with DM. These impacts may include improvements in renal function, wound healing, inflammation reduction, immune modulation, and other metabolic benefits beyond glycemic control (Supplementary Table 2). These findings align with the results of the previous studies in which various non-glycemic effects of MSCs have been examined[37]. Prior studies have confirmed that MSC-based therapies can protect kidneys, as well as regenerate them by creating various conditions, including a decrease in inflammatory infiltrates, reduction of fibrosis, and prevention of glomerulosclerosis, reducing

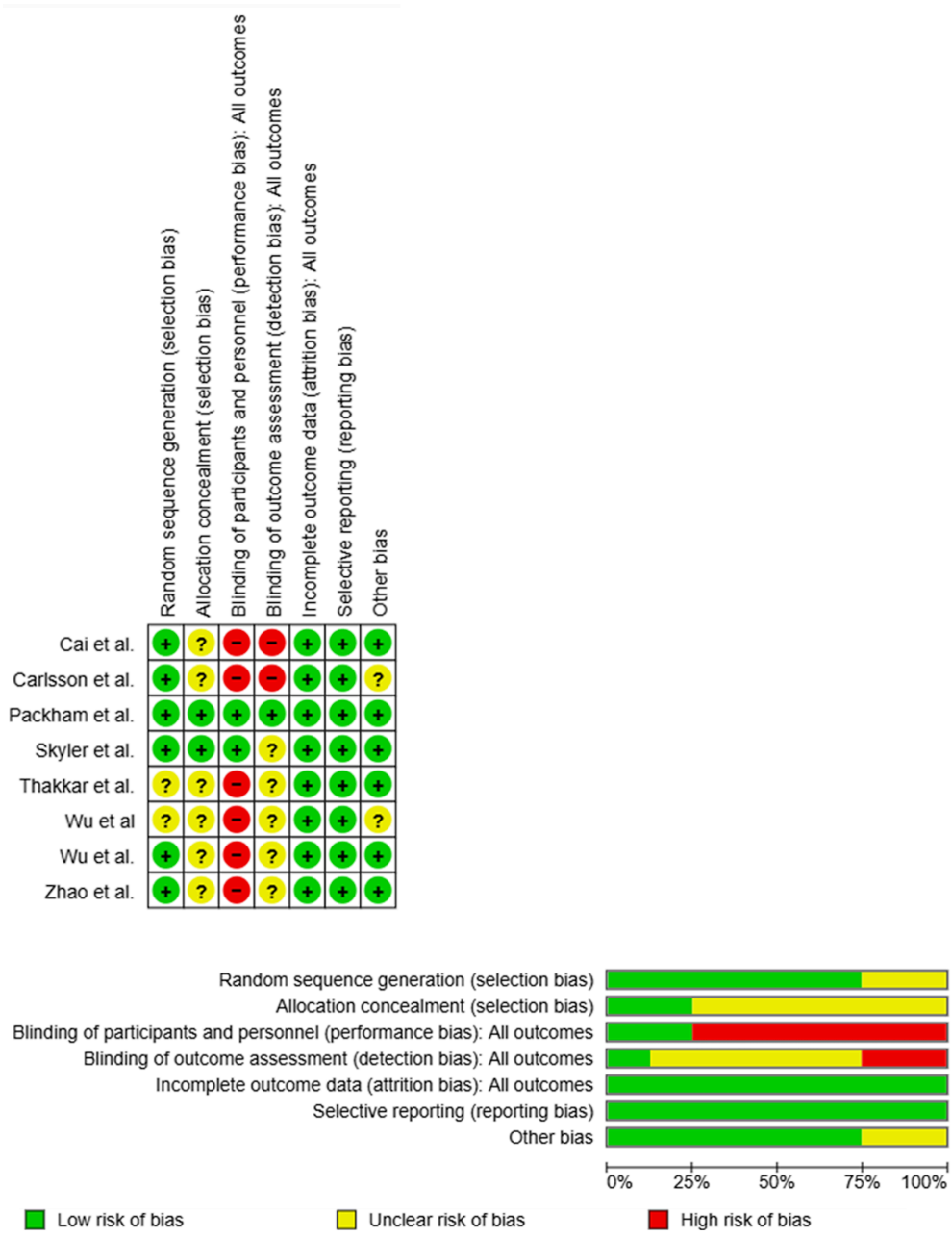


Figure 4 The results of assessment of risk of bias in the studies that underwent meta-analysis.

elevated serum creatinine and blood urea nitrogen levels, and repairing damaged renal tissues and improve renal function by modulating autophagy and fibrotic markers in diabetic conditions[38]. Furthermore, MSC-based therapies may reduce the need for amputations in chronic ischemic wounds and improve overall wound healing outcomes because they promote angiogenesis, reduce inflammation, prevent fibrosis and accelerate tissue repair[39]. Besides, early studies have demonstrated the anti-inflammatory effects of MSC-based therapies[40]. Interestingly, the other function of MSC-based therapies in patients suffering from DM is reducing inflammation by secreting anti-inflammatory molecules such as interleukin-10, transforming growth factor-beta, and tumor necrosis factor-stimulated gene 6, which reduces inflammation-associated diabetic complications[37]. Moreover, MSC-based therapies can modulate both innate and adaptive immune cells, inhibiting autoreactive T cells that contribute to destroying pancreatic beta-cells in type 1 diabetes and preventing the progression of type 1 diabetes[41]. Besides, MSC-based therapies are essential in maintaining immune tolerance and preventing autoimmune attacks on β-cells by promoting the expansion of regulatory T cells[42]. In addition, MSC-based therapies can enhance M2 macrophage polarization, by which resolving inflammation and improving insulin sensitivity in type 2 diabetes can be facilitated[43]. Therefore, as you can see in Figure 6, and based on previous studies and the results of the present study (Supplementary Table 2), it can be inferred that MSC-based therapies affect non-glycemic factors in patients with DM.

The bone marrow is a valuable source of MSCs that affect DM

According to prior studies, bone marrow, due to its immunomodulatory potential, β-cell protection, antigenic capacity,

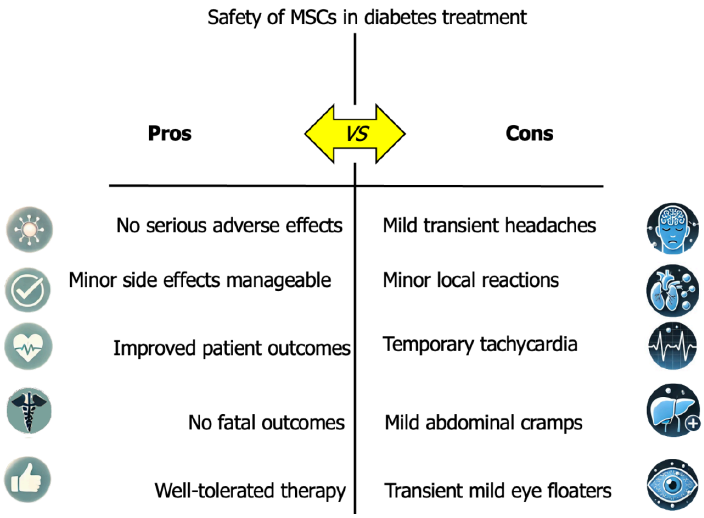


Figure 5 The safety assessment of mesenchymal stem cell-based therapies in patients suffering from diabetes mellitus.

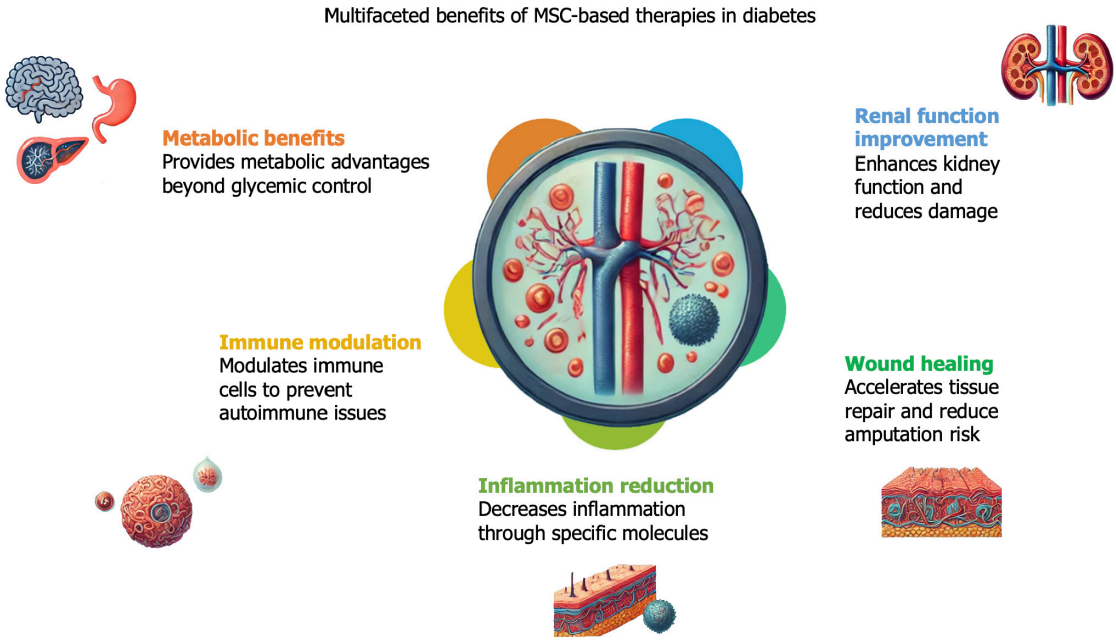


Figure 6 Various non-glycemic effects of mesenchymal stem cell-based therapies on patients with diabetes mellitus. MSC: Mesenchymal stem cell.

and clinical safety, remains a viable and well-researched source for MSC-based therapy in diabetes[44]. Notably, the present scenery has also demonstrated that bone marrow is one of the most used sources for extracting MSCs to treat DM (Table 2). Moreover, based on our meta-analysis, MSCs derived from bone marrow can improve various glycemic factors in patients suffering from DM (Figure 2). Thus, the present study's findings can explain the vast use of bone marrow for MSC-based therapies in patients with DM.

Other source of MSCs that effect on DM

The present study demonstrated that MSCs used for treating DM can be achieved from various sources, including umbilical cord, adipose tissue, placenta, human exfoliated deciduous teeth, and cord blood stem cells (Supplementary Table 2). Notably, previous studies in which the application of MSCs in the treatment of diabetes have been examined and have also demonstrated that various sources, including adipose tissue, umbilical cord, Wharton's jelly and placenta, can be used as valuable sources of MSCs to treat DM[45]. Therefore, based on the present study and previous research, the reasons for using different sources for extracting MSCs to treat DM and the comparison between these sources are mentioned in Table 3.

The effect of allogeneic transplanted MSCs on DM

Allogeneic transplanted MSCs have demonstrated substantial features in treating DM, including reducing inflammation,

Table 3 The reasons for the usage of different sources for extracting mesenchymal stromal cells in order to treat diabetes mellitus[45]

MSC source	Proliferation rate	Immunomodulation	Angiogenesis	Differentiation potential	Clinical applications in diabetes
BM-MSCs	Moderate	Strong	Moderate	Osteogenic, adipogenic, chondrogenic	Immune modulation, islet transplantation support
AD-MSCs	High	Strong	High	Adipogenic, osteogenic, chondrogenic	Insulin sensitivity, wound healing
UC-MSCs	Very high	Strongest	High	Osteogenic, chondrogenic, myogenic	Autoimmune diabetes (T1DM), regenerative therapy
WJ-MSCs	Very high	Strongest	High	Osteogenic, chondrogenic, myogenic	β-cell protection, allogeneic therapy
PD-MSCs	High	Strong	Very high	Multipotent	β-cell protection, neuroprotection, tissue repair

MSC: Mesenchymal stem cell; BM-MSCs: Bone marrow-derived mesenchymal stem cells; AD-MSCs: Adipose tissue derived mesenchymal stem cells; UC-MSCs: Umbilical cord-derived mesenchymal stem cells; T1DM: Type 1 diabetes mellitus; WJ-MSCs: Wharton's jelly mesenchymal stem cells; PD-MSCs: Pluripotent-derived mesenchymal stem cells.

promoting regeneration, anti-fibrotic effects, reducing oxidative stress and modulating immune responses[46]. Therefore, according to all of the mentioned characteristics, allogeneic MSCs have depicted a valuable potential to treat DM. Moreover, the results of the present study, which are demonstrated in Figure 3, along with the findings of previous studies, affirm the high capability of allogeneic MSCs for being utilized to cure DM. However, some findings of the present study about the effects of allogeneic transplanted MSCs on HbA1c and C-peptide levels may contradict the previous relevant studies[47].

The effect of autologous transplanted MSCs on DM

Some studies have confirmed that patients suffering from DM can benefit from autologous MSC therapy because of various capabilities of the mentioned MSCs, including being safe and well tolerated, modulating the immune system, leading to better outcomes with early transplantation, increasing their effectivity by exercise, as well as improving glycemic control by reducing the hypoglycemic episode and enhancing HbA1c levels[48]. Interestingly, our findings have also demonstrated that autologous MSCs can enhance glycemic factors like HbA1c levels, FBG and insulin requirements (Figure 3). Therefore, autologous transplanted MSCs can be a fascinating source for treating DM.

The safety of using MSC-based therapies on patients with DM

Different studies have tried to analyze various side effects and also the fatal effects of MSC-based therapies. In one study in which the safety of MSC-based exosomes has been observed, the results demonstrated that MSC-based therapies, including MSC-based exosomes, lack the potential for direct carcinogenicity and have fewer membrane-bound proteins, which reduce immune reactions[49]. Furthermore, these MSC-based therapies do not mention fatal effects[49]. Supplementary Table 7 in our present study has also demonstrated that MSC-based therapeutic approaches do not have any deadly effects, and this curative approach contains only some minor side effects. Additionally, some studies have mentioned some side effects of MSC-based therapeutic approaches, including thromboembolism and fibrosis, which are common adverse effects in poorly regulated MSC delivery, and organ-specific effects in which MSC therapy has exacerbated pre-existing organ dysfunctions such as renal or liver damage and enhanced tumor growth *via* immunosuppressive and proangiogenic mechanisms[50]. Despite these findings, MSC-based therapies are broadly considered a safe, curative approach for treating different disorders[51]. This fact confirms our findings in Supplementary Table 7.

CONCLUSION

MSC-based therapies present a promising frontier for addressing the complex pathophysiology of DM, particularly in enhancing glycemic control, improving β-cell functionality and reducing dependency on conventional medications. This study highlights the safety and efficacy of MSC-based treatments through systematic evaluation, with findings suggesting minimal adverse effects and significant therapeutic benefits. Moreover, no fatal effects were reported, underscoring the potential of these therapies for broader applications.

FOOTNOTES

Author contributions: Aringazina RA, Zare A, and Tamadon A contributed to the design of the study; Aringazina RA and Zare A contributed to the conception, acquisition, and writing of the manuscript; Mousavi SM and Tamadon A participated in the data analysis

and interpretation; Aringazina RA, Zare A, Abenova N, and Mussin NM contributed to the acquisition and analysis of experimental data and manuscript writing; Aringazina RA, Zare A, Mousavi SM, Abenova N, Mussin NM and Tamadon A contributed to the manuscript revision; Aringazina RA and Tamadon A played key roles in the conceptualization, as well as the writing and revision of the manuscript. Tamadon A will serve as the primary contact for communication with the journal during the manuscript submission, peer review, and publication processes. Tamadon A will be the primary contact for communication with the journal. He is responsible for ensuring the completion of all journal administrative requirements, including providing authorship details, ethics committee approval documentation, clinical trial registration documentation, and gathering conflict-of-interest forms and statements. Moreover, detailed data about the author contributions are mentioned below. All authors have read and approved the final manuscript.

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P-Editor: Zhang XD

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