

REVIEW ARTICLE

Bone marrow- vs. umbilical cord-derived mesenchymal stem cells for type 2 diabetes mellitus treatment: A systematic review and meta-analysis

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Abstract

Background: Contemporary therapeutic options for type-2 diabetes (T2DM) have limitations. We aim to systematically compare the efficacy of bone marrow (BM)- vs. umbilical cord (UC)-derived mesenchymal stem cells (MSCs) for the treatment of T2DM. **Methods:** Four databases were searched to identify five Phase II/III randomized controlled trials (RCTs) and two self-controlled clinical trials (293 patients) that used UC- and BM-derived MSCs to assess their efficacy in T2DM during 3–12 months follow-up. Primary outcomes included glycated hemoglobin (HbA1c), fasting blood glucose (FBG), fasting C-peptide (FCP), and daily exogenous insulin requirement; secondary outcomes included stimulated C-peptide, and homeostatic model assessment for insulin resistance were studied. R software, adopting random-effects meta-analytic models, was used to conduct the primary RCT-restricted (intervention vs. control) and secondary supportive meta-analyses. **Results:** In the primary RCT-restricted analysis, overall pooled effects versus control were frequently heterogeneous and inconsistently significant. However, tissue-source subgroup analyses showed that UC-MSCs had greater reductions in HbA1c and FBG at 6 and 12 months. However, FCP showed preserved or improved levels in UC-MSC arms versus BM-MSC arms at selected time-points. Daily insulin requirements were significantly reduced across all follow-up periods in the intervention groups, without tissue-source superiority. Secondary pre-post analyses supported the overall improvements in glycemic parameters, with recurrent subgroup signals favoring UC-MSCs for HbA1c and FBG. **Conclusion:** Repeated pattern across multiple time-points suggests that UC-MSCs may provide a more consistent glycemic benefit and reductions in insulin requirements. However, methodologically rigorous RCTs directly comparing UC-MSCs and BM-MSCs are necessary to support a recommendation of tissue-source superiority. **Relevance for patients:** These data demonstrate the superiority of UC-MSCs in achieving more durable improvements in glycemic control and reduced exogenous insulin requirements compared to BM-MSCs. However, this needs to be substantiated by further clinical evidence.

Keywords: Bone marrow; Diabetes mellitus; Glycemic control; Mesenchymal stem cells; Meta-analysis; Systematic review; Umbilical cord

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Citation: Al Omar MFS, Alawi YM, Tayara A, *et al.* Bone marrow- vs. umbilical cord-derived mesenchymal stem cells for type 2 diabetes mellitus treatment: A systematic review and meta-analysis. *J Clin Transl Res*. doi: 10.36922/JCTR026150026

Received: April 12, 2026

Revised: May 19, 2026

Accepted: June 2, 2026

Published online: July 2, 2026

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1. Introduction

Diabetes mellitus (DM) is the eighth-leading cause of death worldwide, with a significant increase in prevalence in recent years.¹ As of 2021, the prevalence of DM was 529 million, with type 2 DM (T2DM) accounting for 95.7% of cases, and is expected to reach 1.3 billion by 2025.^{2,3} T2DM is a chronic, multifactorial disease influenced by genetic, environmental, and lifestyle factors that lead to insulin resistance and consistently elevated blood glucose levels.⁴ Despite recent advancements in early detection and treatment of T2DM, the disease typically follows a duration-dependent course, leading to microvascular and macrovascular complications, which are the main culprits of morbidity and mortality in this population.⁵

At best, current therapeutic options for T2DM provide only symptomatic relief. Moreover, after prolonged use, the drugs' effects begin to wane, leading to progressive increases in glycated hemoglobin (HbA1c) and fasting glucose levels.^{6,7} Over the course of the disease, pancreatic β -cell function steadily declines at a rate of 4–5% per year, independent of glucose control, with no treatment to reverse this decline.^{8,9} These cellular and organ-level changes lead to a progressive, stepwise intensification of therapy, with possible addition of insulin injections, thereby increasing cost and reducing quality of life. These factors may adversely affect treatment adherence and overall patient compliance.^{10,11}

The use of mesenchymal stem cells (MSCs) is emerging as a curative strategy for T2DM through the regeneration of β -cells and the enhancement of tissue insulin sensitivity.¹² MSCs also have immunomodulatory and anti-inflammatory properties that address the chronic systemic inflammation in T2DM.¹³ Other studies have reported glycemic improvement, including decreased HbA1c, lower insulin dose requirements, and fewer complications observed with high-intensity therapy.^{14,15} The most important primary outcome highlighting the value of MSC therapy is glycemic control, measured by HbA1c% and fasting blood glucose (FBG).¹⁴ Secondary outcomes, such as insulin resistance (homeostatic model assessment for insulin resistance; HOMA-IR) and daily insulin requirements, inflammatory marker levels (C-reactive protein, interleukin-6, tumor necrosis factor- α), and the incidence of diabetic complications, are important parameters to consider.¹⁶

The biology and clinical efficacy of MSCs vary significantly across tissue sources.¹⁷ Umbilical cord (UC)-MSCs are obtained non-invasively, have higher proliferative capacity, and are rich in a primitive stem cell population with a lower senescence rate, homogeneous potency, and

strong immunomodulatory effects.^{18–21} Conversely, bone marrow (BM)-MSCs are obtained more invasively and display slower proliferative capacity, a higher senescence rate, variable potency, and weaker immunomodulatory effects.^{18–21} Despite these differences, both cell types have shown promising safety and therapeutic efficacy in clinical settings.²² A recently published meta-analysis of MSCs from different tissue sources has grouped them into a single pooled analysis to report their efficacy, albeit without delineating the effect of tissue source on efficacy.²³

To our knowledge, our study is the first to report a direct systematic comparison of MSCs from the two tissue sources in T2DM patients, with time-specific responses across multiple follow-up time points. It involves a network meta-analysis comparing randomized controlled trials (RCTs) using BM-MSCs and UC-MSCs, and a secondary analysis combining RCTs with self-controlled trials to analyze the overall effect of the two cell types by comparing baseline and follow-up clinical parameters.

2. Methods

2.1. Protocol registration and search strategy

This study (PROSPERO ID: RD420251238567) adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses-2020 checklist.²⁴ The Cochrane Handbook guidelines for Systematic Reviews and Meta-analysis were followed in the methods and analyses.²⁵ Four databases, including PubMed, Springer Nature, ClinicalTrials, and the Cochrane Library, were used to identify studies on BM-MSCs and UC-MSCs and their clinical effects in patients with T2DM. Keywords used to ensure adequate coverage of published studies, such as “Mesenchymal stem cells,” “BM-MSCs,” “UC-MSCs,” “Type 2 Diabetes Mellitus,” and “Diabetes mellitus type 2.” Two independent authors conducted the screening process online in Google Sheets, with a tiebreaker in the event of any decision differences. Duplicates were removed across different databases using the built-in Google Document feature and by manually checking registration-related data.

2.2. Eligibility criteria

Study inclusion was based on a pre-defined model of participants, interventions, comparisons, outcomes, and study design (PICOS), as listed. Studies were considered fit if they met all elements in the listed criteria:

- Participants: patients with T2DM, regardless of age, sex, gender, or race.
- Intervention: BM-MSCs or UC-MSCs.
- Comparison: Control arm (placebo or standard care) or self-controlled (one group undergoes the

intervention and compares the results with the baseline).

- Outcome: Clinical and metabolic outcomes (e.g., glycemic control, insulin requirement, fasting C-peptide [FCP], etc.).
- Study design: phase II or III randomized controlled trials, or self-controlled trials.

Studies conducted on animals or published in a non-English language were excluded. Phase I trials, observational studies, case reports, reviews, or conference abstracts without full data, or studies not involving MSCs were also excluded.

2.3. Data extraction process

The studies were divided into two parts; each part was handled by two authors, who independently extracted the data, and a third author served as the determiner. All extractors used the same standardized form online on Google Sheets. The form contains information on the characteristics of each included study: study ID, location, phase, intervention, stem cell type and dose, sample size, mean sample age, baseline characteristics of the cohort, follow-up period, comorbidities, and outcomes of interest. If the outcome data were continuous, we used the mean and standard deviation. When studies reported continuous outcomes as medians and interquartile ranges, means and standard deviations were estimated using established methods.^{26,27} When numerical data were not reported, values were extracted from published figures using WebPlotDigitizer tools²⁸, and when studies reported data as box plots, means and standard deviations were estimated from medians and interquartile ranges using established methods. MSC arms were combined into a single intervention group to avoid double-counting the control group and to preserve the independence of effect sizes, following recommendations in the Cochrane Handbook.²⁵ Combined means and standard deviations were calculated using sample-size-weighted formulas. To minimize potential inaccuracies in graph-derived values, extracted data were checked against the published figures and interpreted with caution as approximate estimates when numerical values were unavailable.

2.4. Risk of bias assessment

Two independent authors used the Cochrane Risk of Bias 2 (RoB2) and Cochrane Risk of Bias 1 V2 tools, respectively, to assess the quality of RCT and non-RCT studies. A third author resolved discrepancies between the primary two authors.

2.5. Outcome definitions

Efficacy of MSC-based therapy was assessed by analyzing

the extent of change from baseline in the primary outcomes of interest, including HbA1c (%), FBG (mg/dL), FCP (ng/mL), and exogenous insulin requirement (U/day). Secondary outcomes measured were stimulated C-peptide (ng/mL) and HOMA-IR (%). These changes were pooled as a mean difference (MD) in a meta-analysis model and analyzed at 3, 6, and 12 months.

2.6. Statistical analysis

All meta-analyses were conducted in R software (Version 4.5.2, R Core Team, Austria) using established meta-analysis packages. The primary analysis was a Network Meta-Analysis (NMA) restricted to RCTs, which estimated pooled treatment effects of UC-MSC vs BM-MSC, making the subgroup meta-analysis by cell source (UC vs BM) the main comparison of interest. A secondary (supportive) analysis pooled all eligible studies to summarize the magnitude of improvement from baseline to follow-up within MSC arms (with the same UC vs BM subgroup structure), intended to complement the primary RCT-based comparative NMA. For continuous outcomes, effect sizes were calculated as MDs when outcomes were measured on the same scale, each with 95% confidence intervals (CIs). Given the expected clinical and methodological diversity, pooled estimates were obtained using a prespecified random-effects model; therefore, fixed-effect sensitivity was not emphasized.²⁵ Statistical heterogeneity was evaluated using the I^2 statistic, with significance assessed by the p-value of the Cochrane Q test. We interpreted I^2 values of approximately 0% as no observed heterogeneity, ~25% as low, 50–75% as moderate, and >75% as high heterogeneity.²⁵

Sensitivity analyses were not performed because the evidence base for most outcomes and time points was extremely limited, with few studies. In several analyses, only one or two trials contributed to the data for a given outcome/time point (and within the UC-MSC and BM-MSC subgroups), rendering conventional sensitivity analyses uninformative or potentially misleading. Consequently, any apparent lack of “robustness” would not reflect a meaningful test of reliability across the body of evidence. Hence, we prioritized transparent reporting of the pooled effects with random-effects methods, alongside careful interpretation of confidence intervals, heterogeneity statistics, and the limited power to detect subgroup differences, and we explicitly treat these findings as preliminary.

We also did not perform a design-restriction sensitivity analysis for the pre-post meta-analyses because RCT-only effects had already been highlighted and presented in the primary analysis. The secondary analysis was intended to

be supportive, complementary evidence to the primary analysis. However, the inclusion of nonrandomized designs may influence the pooled baseline-to-follow-up changes. Assessment of publication bias (e.g., funnel plots or Egger's test) and meta-regression were not performed due to the small number of studies available for most outcomes (<10). Subgroup analyses were performed by stem cell source (UC-MSCs vs BM-MSCs) and by follow-up duration (3, 6, and 12 months). We pooled outcomes measured at comparable time points during close follow-up. When multiple time points were reported, we extracted the time point closest to the prespecified follow-up windows (e.g., ~3 months and ~6 months). We conducted separate meta-analyses for each time point. We avoided pooling across substantially different follow-up durations to minimize time-related heterogeneity. When a subgroup contained only one study, the subgroup estimate was considered descriptive and exploratory rather than definitive comparative. Similarly, statistically significant subgroup findings in the presence of non-significant overall effects were interpreted as possible tissue-source signals rather than conclusive evidence of superiority, especially given the small number of trials, heterogeneity, and repeated time-point analyses.

3. Results

3.1. Characteristics of the included studies

Our literature search identified 544 records across multiple databases. A total of 20 duplicates and 501 records that did not meet the eligibility criteria, and a further 16 studies were removed due to multiple reasons, as shown in Figure 1. Five RCTs and two self-controlled trials published between 2014 and 2022 were included in the meta-analysis (Table S1). These studies were conducted in China ($n = 4$), India ($n = 2$), and the United States ($n = 1$) (Table S1). The intervention arms included UC-MSC ($n = 4$) or BM-MSC ($n = 3$) treatment, with a total of 293 participants. A cell dose of 1×10^6 cells/kg in the intervention arms was relatively consistent across studies, with follow-up periods ranging from 3 to 12 months. The route and schedule of administration were not fully identical across trials. UC-MSC studies generally used peripheral intravenous infusions, often repeated at fixed intervals. In contrast, BM-derived cell interventions were delivered either intravenously or, in some BM-derived protocols, by targeted pancreatic arterial infusion (Table S1).

Tables S2 and S3 summarize the baseline characteristics of study participants, which were generally comparable

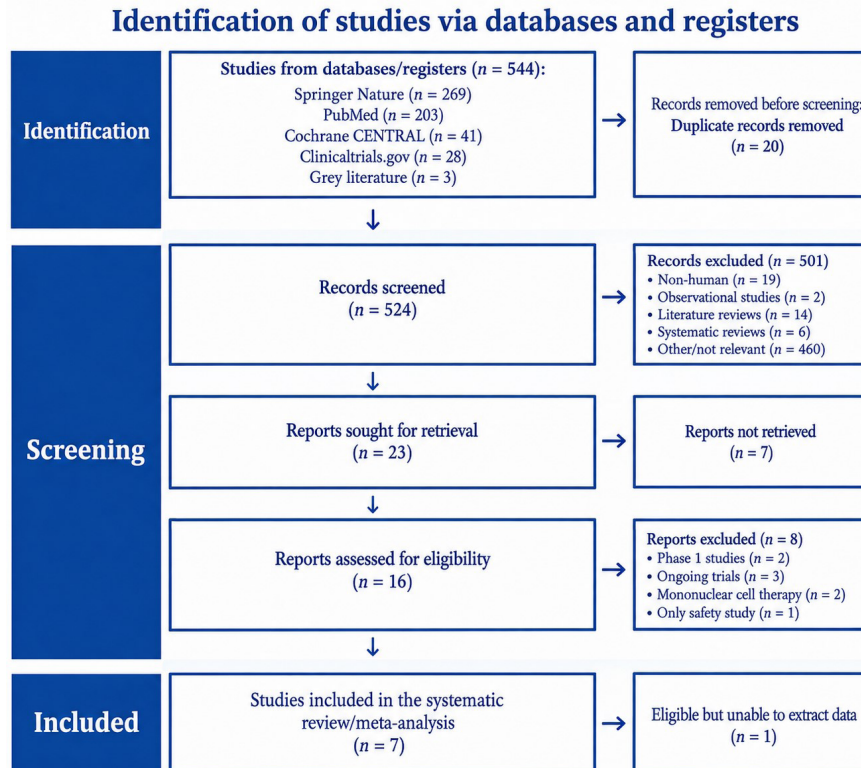


Figure 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram for the screening and selection of eligible trials

between intervention and control groups within each RCT. Most studies reported elevated baseline HbA1C and FBG levels, indicating poor glycemic control, whereas baseline fasting C-peptide levels were heterogeneous across trials. Daily insulin requirements varied widely across the intervention arms. HOMA-IR was reported in multiple studies and similarly showed variability. Stimulated C-peptide levels highlighted heterogeneity in baseline residual β -cell function.

3.2. Risk of bias assessment

Using RoB2, the overall risk of bias across RCTs varied by study. Bhansali *et al.*²⁹ reported low risk, whereas Hu *et al.*³⁰ raised some concerns. In contrast, three studies, including Bhansali *et al.*³¹, Skyler *et al.*³², and Zang *et al.*³³, had a high risk of bias, mainly due to the high risk in the measurement of the outcome. Using Risk Of Bias In Non-randomized Studies of Interventions-1, the overall risk of bias among the non-RCTs was serious in Liu *et al.*³⁴ and

Lian *et al.*³⁵, mainly due to confounding and participant selection (Figures 2 and 3).

3.3. Treatment efficacy (primary analysis)

3.3.1. Glycated hemoglobin assessment during follow-up

Across follow-up timepoints, pooled analysis showed no significant overall difference in HbA1c between treatment and control groups at 3 months (MD: -0.05% , 95% confidence interval [CI]: -0.65 – 0.55), 6 months (MD: -0.37 , 95% CI: -0.37 – 0.42), or 12 months (MD: -0.44 , 95% CI: -1.01 – 0.13). Heterogeneity was considerable across all timepoints, with $I^2 = 87.5\%$, $p < 0.0001$ at 3 months, $I^2 = 91.9\%$, $p = 0.0001$ at 6 months, and $I^2 = 80.9\%$, $p = 0.0013$ at 12 months. Subgroup-difference testing was not significant at 3 months ($\chi^2 = 3.23$, $p = 0.0725$), but became significant at 6 months ($\chi^2 = 5.33$, $p = 0.021$) and 12 months ($\chi^2 = 10.08$, $p = 0.0013$).

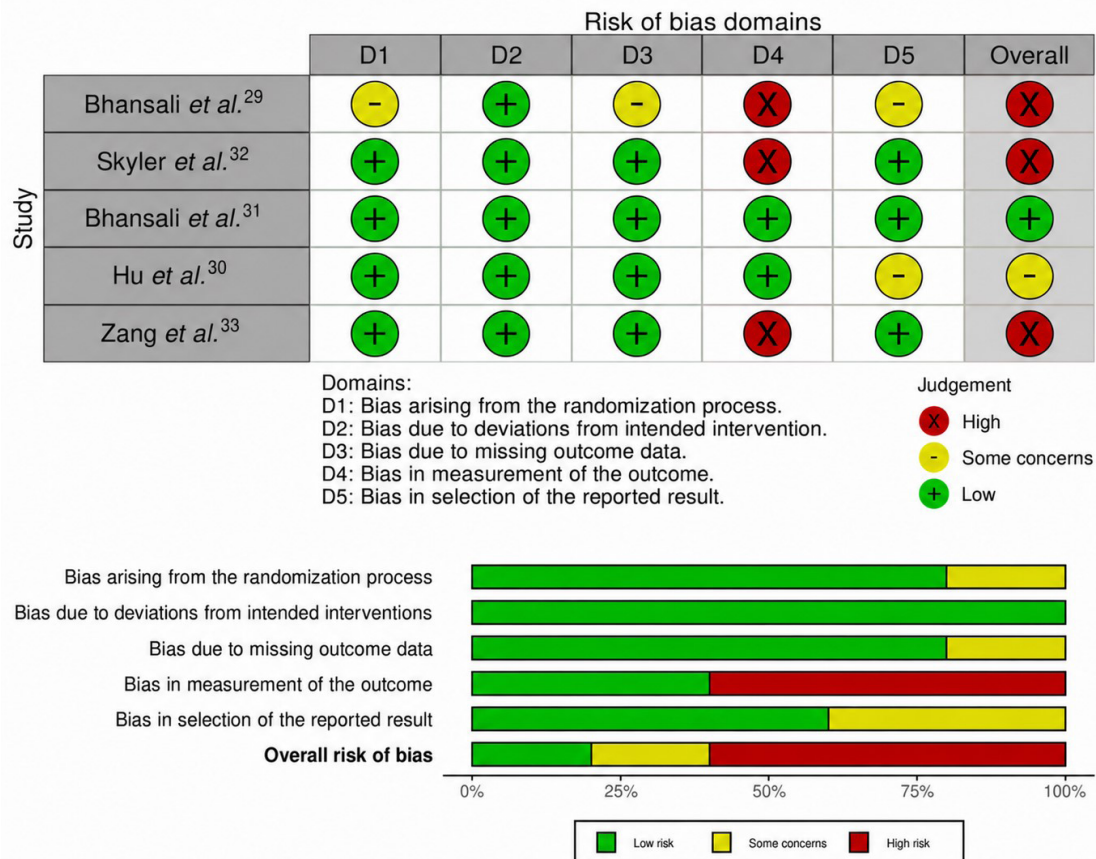


Figure 2. Risk of bias (quality) of the randomized controlled trials included in the analysis using the Cochrane Risk of Bias 2 tool

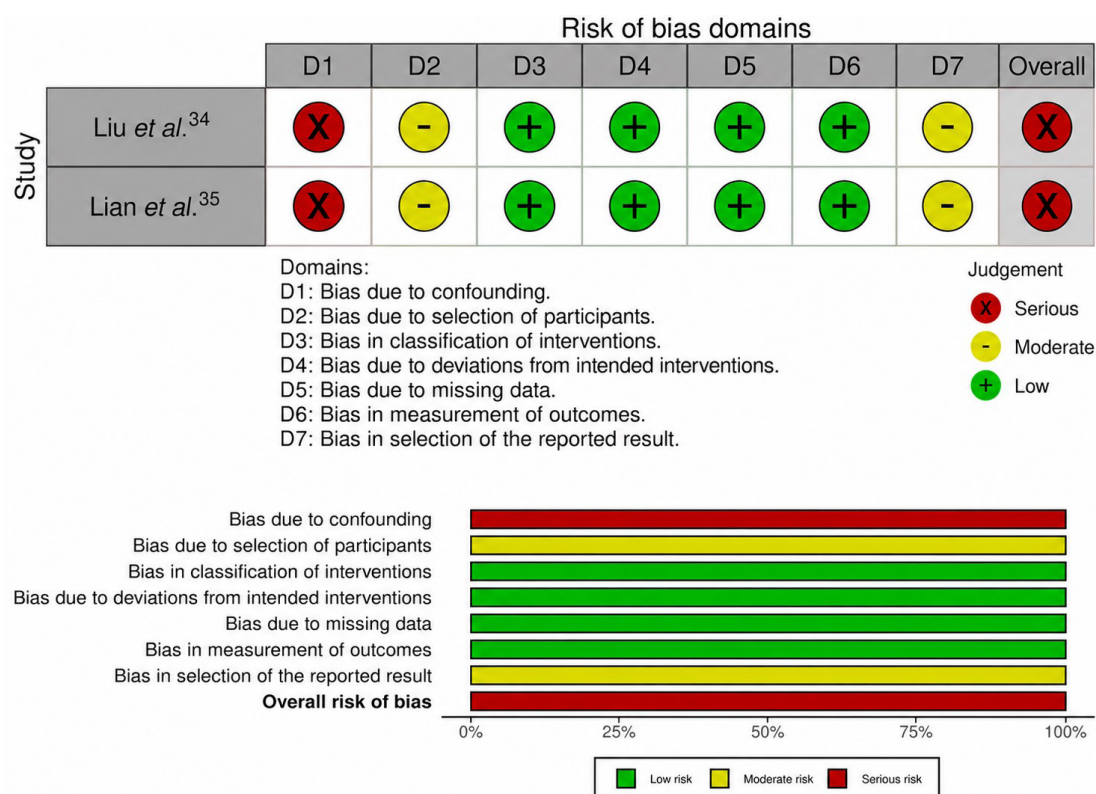


Figure 3. Risk of bias (quality) of non-randomized controlled trials included in the analysis using the Cochrane Risk of Bias 1 V2 tool

In the subgroup analyses, UC-MSC showed a significant reduction in HbA1c at all assessed time points, with MDs of -0.47 (95% CI: -0.75 – -0.19) at 3 months, -0.96 (95% CI: -1.61 – -0.32) at 6 months, and -0.89 (95% CI: -1.29 – -0.48) at 12 months. In contrast, BM-MSC showed no significant effect at any time point, with MDs of 0.37 (95% CI: -0.50 – 1.24) at 3 months, 0.23 (95% CI: -0.55 – 1.02) at 6 months, and 0.06 (95% CI: -0.36 – 0.48) at 12 months. Heterogeneity within the UC-MSC subgroup was $I^2 = 0\%$, $p = 0.3395$ at 3 months, $I^2 = 78.9\%$, $p = 0.0295$ at 6 months, and $I^2 = 48.2\%$, $p = 0.1647$ at 12 months, while within the BM-MSC subgroup it was $I^2 = 92.2\%$, $p = 0.0004$ at 3 months, $I^2 = 77.9\%$, $p = 0.0335$ at 6 months, and $I^2 = 0$, $p = 0.5469$ at 12 months (Figure 4A–4C). Overall, UC-MSC showed a consistent advantage over BM-MSC in reducing HbA1c over the follow-up period, but the pooled effect was not significant.

3.3.2. Fasting blood glucose assessment during follow-up

Across the assessed follow-up timepoints, pooled analysis showed no statistically significant overall difference in FBG between MSC-treated and control groups at 3 months

(MD: -9.57 , 95% CI: -29.2 – 10.06), 6 months (MD: -6.76 , 95% CI: -21.23 – 7.71), or 12 months (MD: -4.29 , 95% CI: -22.62 – 14.05). Heterogeneity was substantial at all three time points, with $I^2 = 90.2\%$, $p \leq 0.0001$ at 3 months, $I^2 = 84.5\%$, $p = 0.0016$ at 6 months, and $I^2 = 93.5\%$, $p \leq 0.0001$ at 12 months. Subgroup-difference testing was not significant at 3 months ($\chi^2 = 3.59$, $p = 0.058$), but became significant at 6 months ($\chi^2 = 12.4$, $p = 0.0004$) and was strongly significant at 12 months ($\chi^2 = 29.03$, $p \leq 0.0001$).

In subgroup analyses, the pooled UC-MSC subgroup estimate showed a significant reduction in FBG at all assessed time points, with MD: -24.28 (95% CI: -30.4 – -18.16) at 3 months, MD: -18.57 (95% CI: -23.79 – -13.35) at 6 months, and MD: -21.43 (95% CI: -27.23 – -15.63) at 12 months. In contrast, the pooled BM-MSC subgroup estimate showed no significant effect, with MDs of -0.12 (95% CI: -24.34 – 24.1) at 3 months, 1.43 (95% CI: -8.41 – 11.27) at 6 months, and 5.34 (95% CI: -2.48 – 13.16) at 12 months. Heterogeneity within the BM-MSC subgroup was $I^2 = 60.5\%$, $p = 0.1114$ at 3 months, $I^2 = 0$, $p = 0.4743$ at 6 months, and $I^2 = 3.8\%$, $p = 0.3078$ at 12 months, whereas the UC-MSC subgroup consisted of a single study at each time point (Figure 5A–5C). Overall, these findings suggest

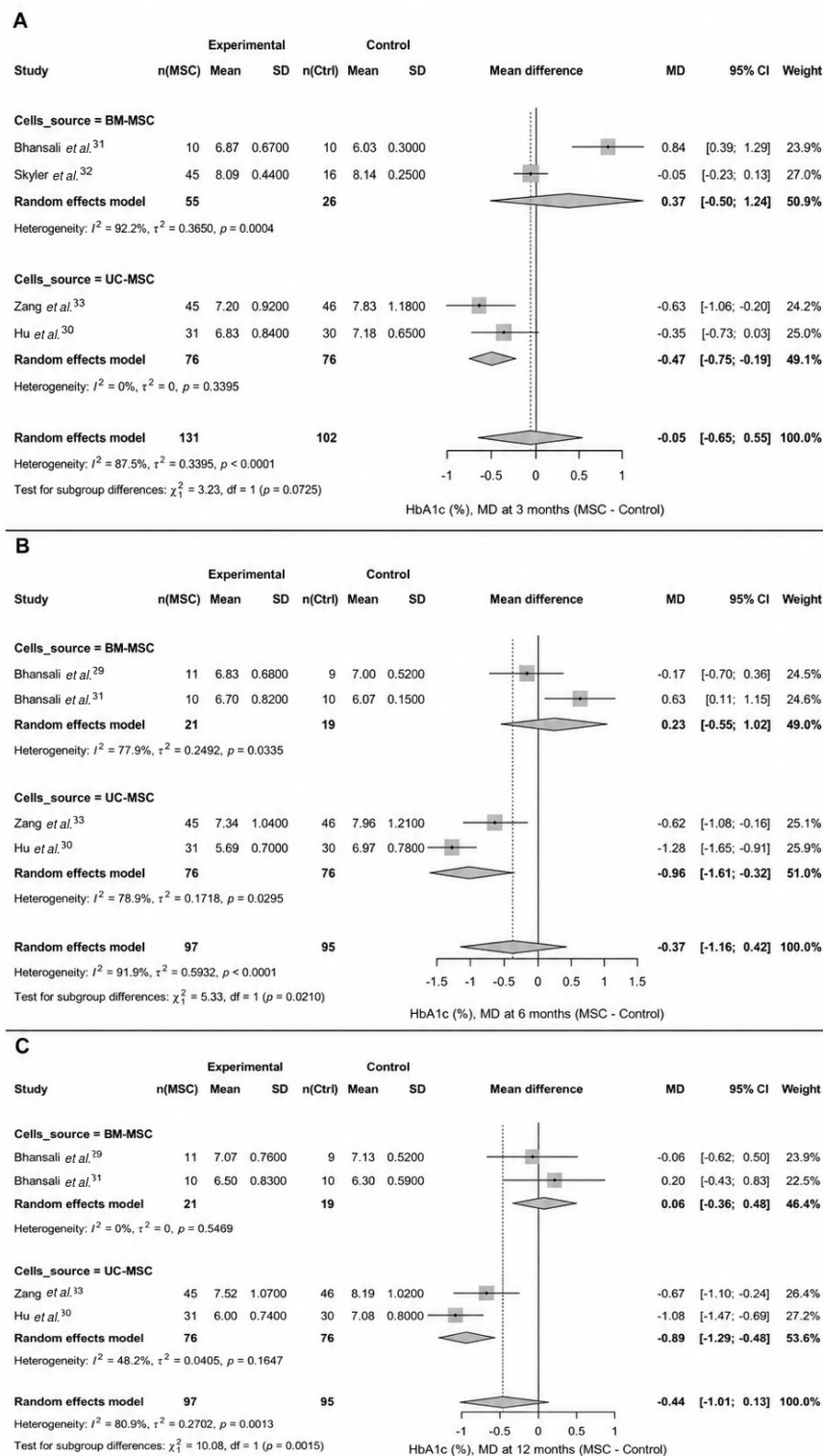


Figure 4. Primary analysis, Hb1Ac assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

a clearer benefit of UC-MSC over BM-MSC in reducing FBG across follow-up periods, despite non-significant pooled comparisons.

3.3.3. Fasting C-peptide assessment during follow-up

Across the evaluated follow-up timepoints, pooled analysis showed no statistically significant overall difference in FCP between MSC-treated and control groups at 3 months (MD: -0.12, 95% CI: -0.88–0.63), 6 months (MD: 0.34, 95% CI: -0.29–0.96), and 12 months (MD: 0.18, 95% CI: -0.79–1.16). Heterogeneity remained high across the three time points, with $I^2 = 93\%$, $p < 0.0001$ at 3 months, $I^2 = 94\%$, $p < 0.0001$ at 6 months, and $I^2 = 95.1\%$, $p < 0.0001$ at 12 months. Subgroup-difference testing was statistically significant at 3 months ($\chi^2 = 13.31$, $p = 0.0003$), not significant at 6 months ($\chi^2 = 3.26$, $p = 0.071$), and became significant again at 12 months ($\chi^2 = 6.7$, $p < 0.0096$).

In subgroup analyses, BM-MSC showed a negative reduction in FCP across all time points, with MDs of -0.83 (95% CI: -1.3–-0.36) at 3 months, -0.2 (95% CI: -0.7–0.3) at 6 months, and -0.8 (95% CI: -1.55–0.05) at 12 months. In contrast, UC-MSC showed statistically insignificant increase of FCP with MD: 0.47 (95% CI: -0.04–0.97) at 3 months, MD: 0.57 (95% CI: -0.1–1.23) at 6 months, and MD: 0.6 (95% CI: -0.15–1.36) at 12 months. Heterogeneity within the BM-MSC subgroup was $I^2 = 0\%$, $p = 0.6812$ at 3 months, while within the UC-MSC subgroup it was $I^2 = 89.8\%$, $p = 0.0018$ at 3 months, $I^2 = 95.3\%$, $p < 0.0001$ at 6 months; and $I^2 = 95.8\%$, $p < 0.0001$ at 12 months (Figure 6A–6C). Overall, FCP did not show a pooled significant benefit of MSC therapy over control.

However, subgroup analyses showed a recurrent exploratory pattern favoring UC-MSC over BM-MSC across follow-up periods, which should be interpreted cautiously given heterogeneity and limited sample size.

3.3.4. Daily insulin requirement during follow-up

Across follow-up timepoints, pooled analysis showed a statistically significant reduction in daily insulin requirement in MSC-treated patients compared-control group at all assessed time points, with pooled effect estimates at 3 months (MD: -14.91, 95% CI: -19.82–-10.00), 6 months (MD: -15.84, 95% CI: -24.91–-6.78), and 12 months (MD: -19.41, 95% CI: -29.45–-9.38). Heterogeneity was $I^2 = 30\%$, $p = 0.2383$ at 3 months, $I^2 = 85.2\%$, $p = 0.0002$ at 6 months, and $I^2 = 82.3\%$, $p = 0.0007$ at 12 months.

Subgroup-difference testing was not significant at any time point, with $\chi^2 = 0.03$, $p = 0.08681$ at 3 months, $\chi^2 = 0.13$, $p = 0.1743$ at 6 months, and $\chi^2 = 0.07$, $p = 0.7886$ at 12 months. In subgroup analyses, UC-MSC showed a

significant reduction in insulin requirement at 3 months with MD: -14.65 (95% CI: -20.4–-8.89), an insignificant reduction at 6 months with MD: -16.78 (95% CI: -33.62–0.05), and a significant reduction at 12 months with MD: -19.41 (95% CI: -29.48–-9.38). BM-MSC showed a significant reduction across all time points, except at 3 months, with MDs of -16.26 (95% CI: -34.41–1.89) at 3 months, -13.16 (95% CI: -22.78–-3.54) at 6 months, and -16.97 (95% CI: -29.79–-4.16) at 12 months. Heterogeneity within the UC-MSC subgroup was $I^2 = 65.1\%$, $p = 0.0904$ at 3 months, $I^2 = 93.7\%$, $p < 0.0001$ at 6 months, and $I^2 = 93.1\%$, $p = 0.0001$ at 12 months, whereas within the BM-MSC subgroup it was not reported at 3 months because that subgroup contained a single study, and was $I^2 = 0$, $p = 0.5548$ at 6 months and $I^2 = 0$, $p = 0.4699$ at 12 months (Figure 7A–7C). Overall, there was a sustained reduction in daily insulin requirement with MSC therapy, with no significant difference between the two cell sources.

3.3.5. Glucagon stimulated C-peptide during follow-up

Across the assessed follow-up time points, the pooled analysis showed no statistically significant overall difference in glucagon-stimulated C-peptide between the MSC-treated and control groups, with pooled effect estimates at 6 months (MD: 0.21, 95% CI: -0.68–1.11) and 12 months (MD: 0.27, 95% CI: -0.37–0.91). Heterogeneity was moderate to substantial, with $I^2 = 63.3\%$, $p = 0.0654$ at 6 months and $I^2 = 67.4\%$, $p = 0.0467$ at 12 months. Subgroup-difference testing was not significant at either time point, with $\chi^2 = 0.06$, $p = 0.8018$ at 6 months and $\chi^2 = 0.23$, $p = 0.6307$ at 12 months.

In subgroup analyses, BM-MSC showed MD: 0.34 (95% CI: -1.55–2.23) at 6 months and MD: 0.42 (95% CI: -0.83–1.66) at 12 months, while the single UC-MSC study showed MD: 0.1 (95% CI: -0.09–0.29) at 6 months and MD: 0.11 (95% CI: -0.08–0.3) at 12 months. Heterogeneity within the BM-MSC subgroup was $I^2 = 81.2\%$, $p = 0.021$ at 6 months and $I^2 = 81.6\%$, $p = 0.0196$ at 12 months, whereas the UC-MSC subgroup consisted of a single study at both time points (Figure 8A–8B). Overall, MSC therapy did not significantly affect glucagon-stimulated C-peptide during follow-up.

3.3.6. Homeostatic model assessment for insulin resistance during follow-up

Across the evaluated follow-up time points, the pooled analysis of HOMA-IR suggested a significant improvement at 6 months but not at 12 months, with pooled effect estimates at 6 months (MD: -0.23, 95% CI: -0.39–-0.07) and at 12 months (MD: -1.73, 95% CI: -5.25–1.78).

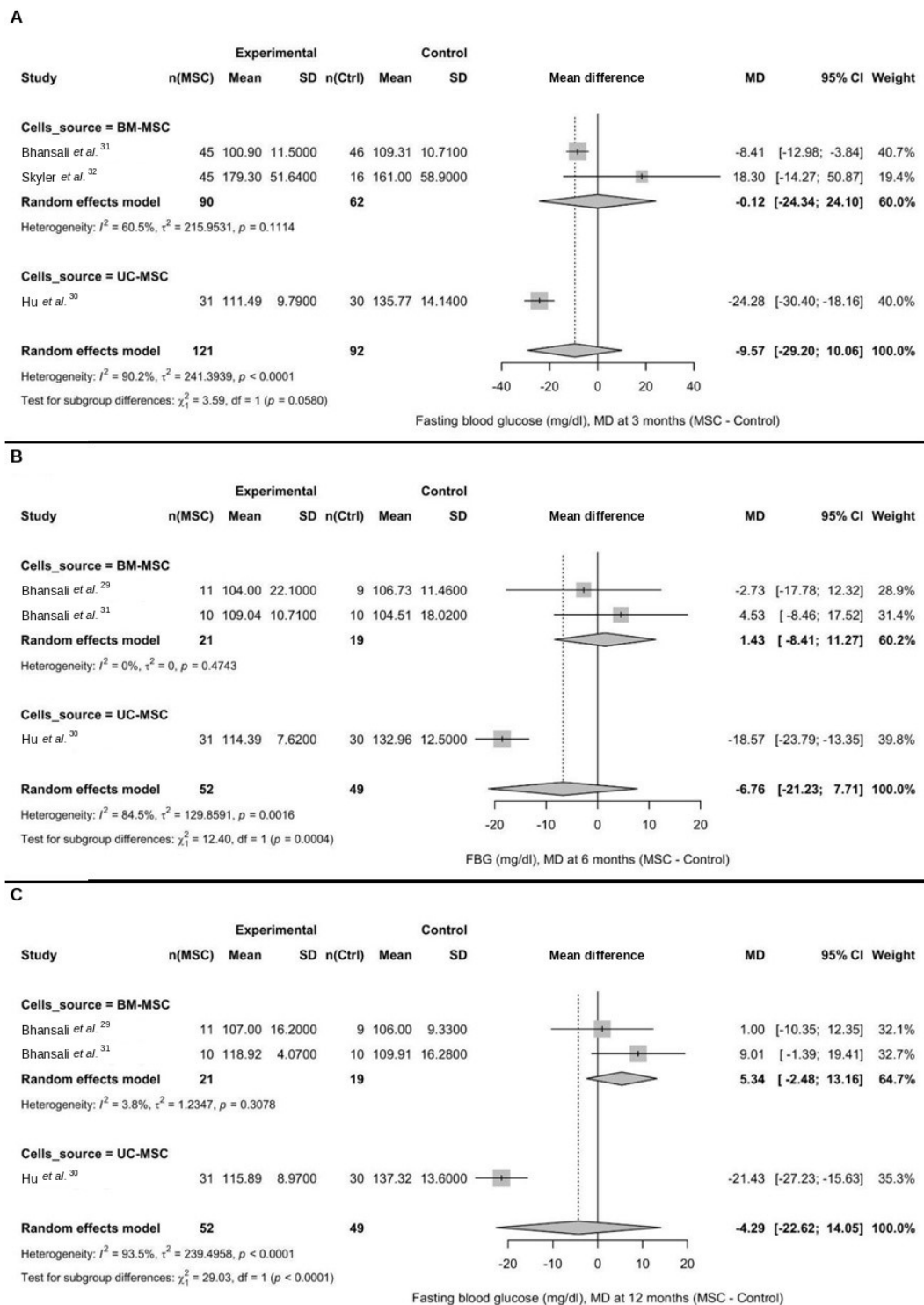


Figure 5. Primary analysis, fasting blood glucose assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

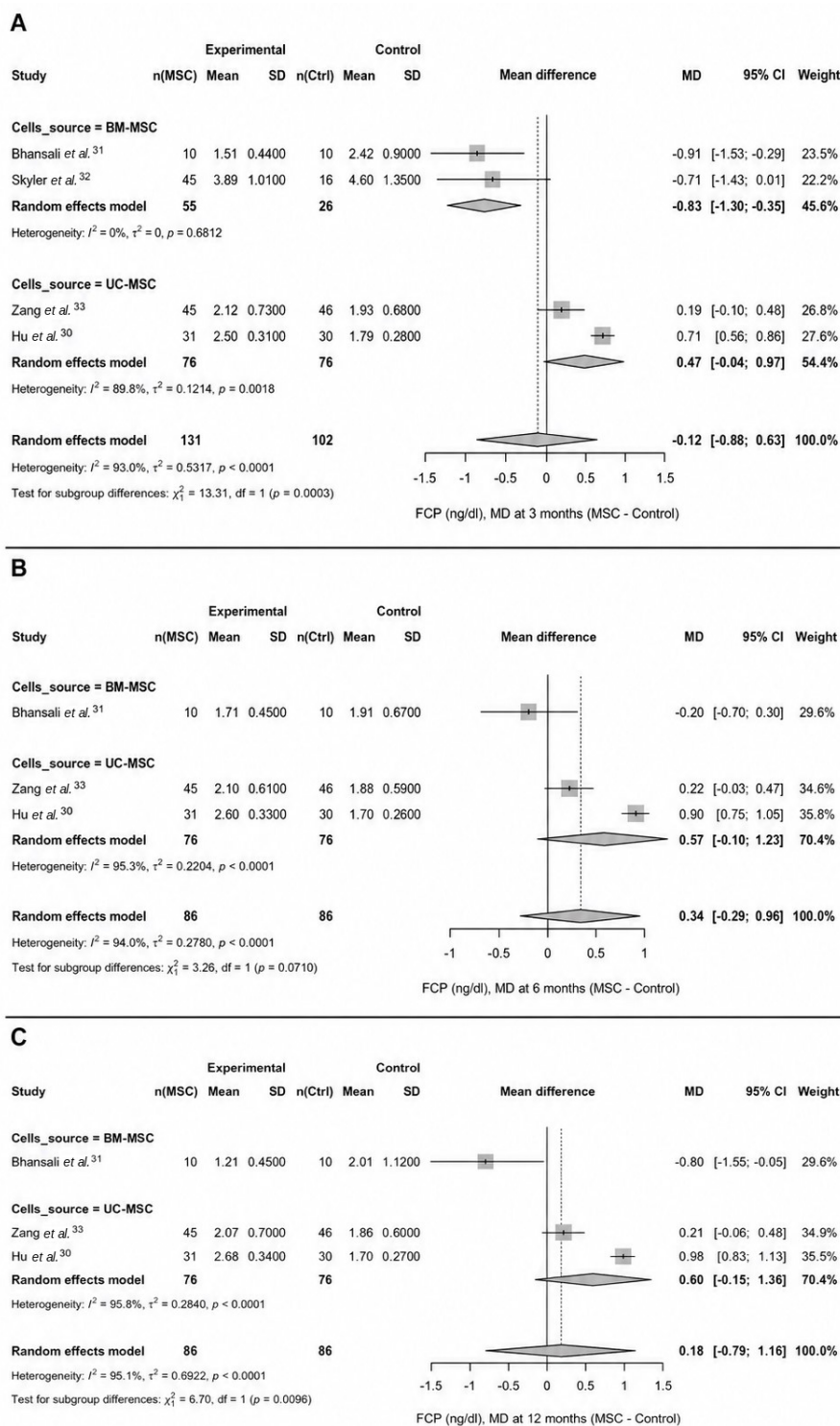
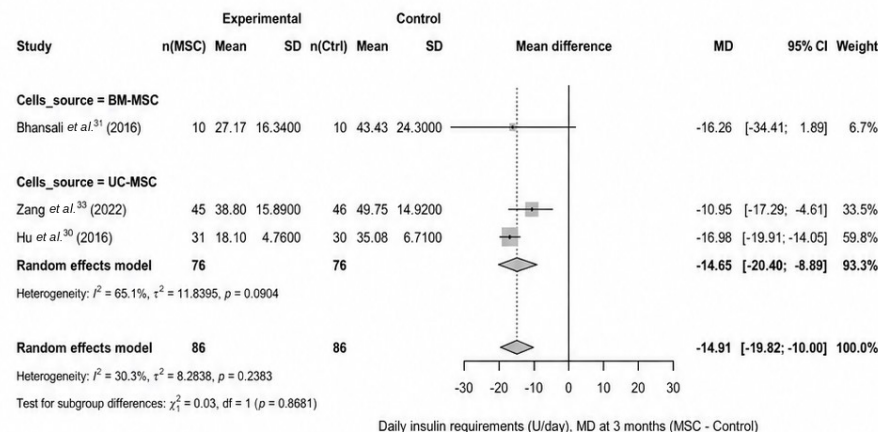


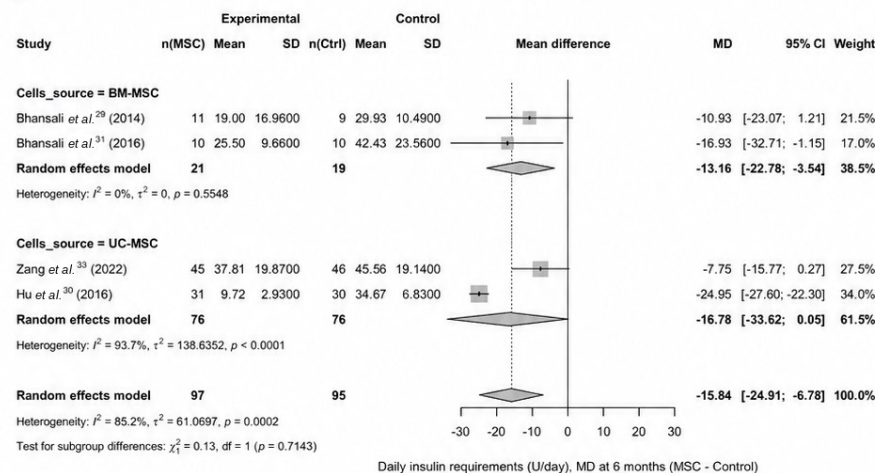
Figure 6. Primary analysis, FCP assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; FCP: Fasting C-peptide; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

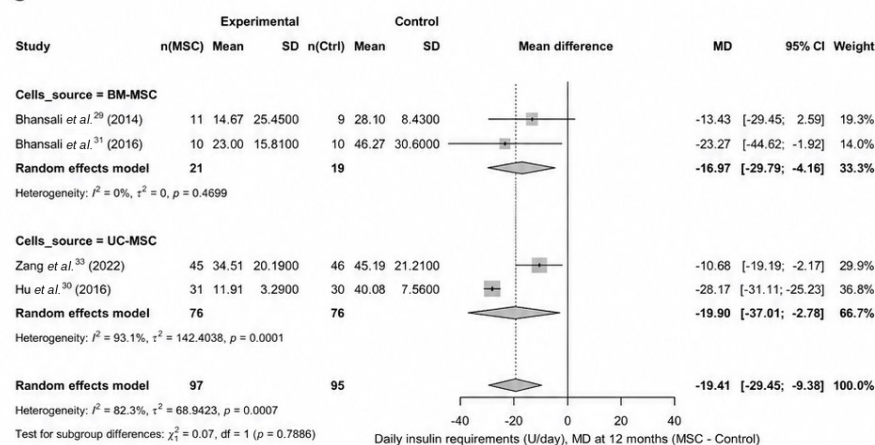
A



B



C

**Figure 7.** Primary analysis, daily insulin requirements assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

Heterogeneity was substantial at both time points, with $I^2 = 73\%$ and $p = 0.0246$ at 6 months, and $I^2 = 84.1$ and $p = 0.0018$ at 12 months. Subgroup-difference testing was not significant at either time point, with $\chi^2 = 0.77$, $p = 0.3808$ at 6 months and $\chi^2 = 1.16$, $p = 0.281$ at 12 months. In subgroup analyses, BM-MSC showed MD: -3.19 (95% CI: $-9.83-3.45$) at 6 months and MD: -3.34 (95% CI: $-9.6-2.93$) at 12

months, whereas the single UC-MSC study showed MD: -0.22 (95% CI: $-0.39--0.05$) at 6 months and MD: 0.11 (95% CI: $-0.04-0.26$) at 12 months. Heterogeneity within the BM-MSC subgroup was $I^2 = 86.4\%$, $p = 0.0067$ at 6 months and $I^2 = 84.1\%$, $p = 0.0121$ at 12 months, while the UC-MSC subgroup consisted of a single study at both time points (Figure 9A–9B). Overall, these findings suggest that

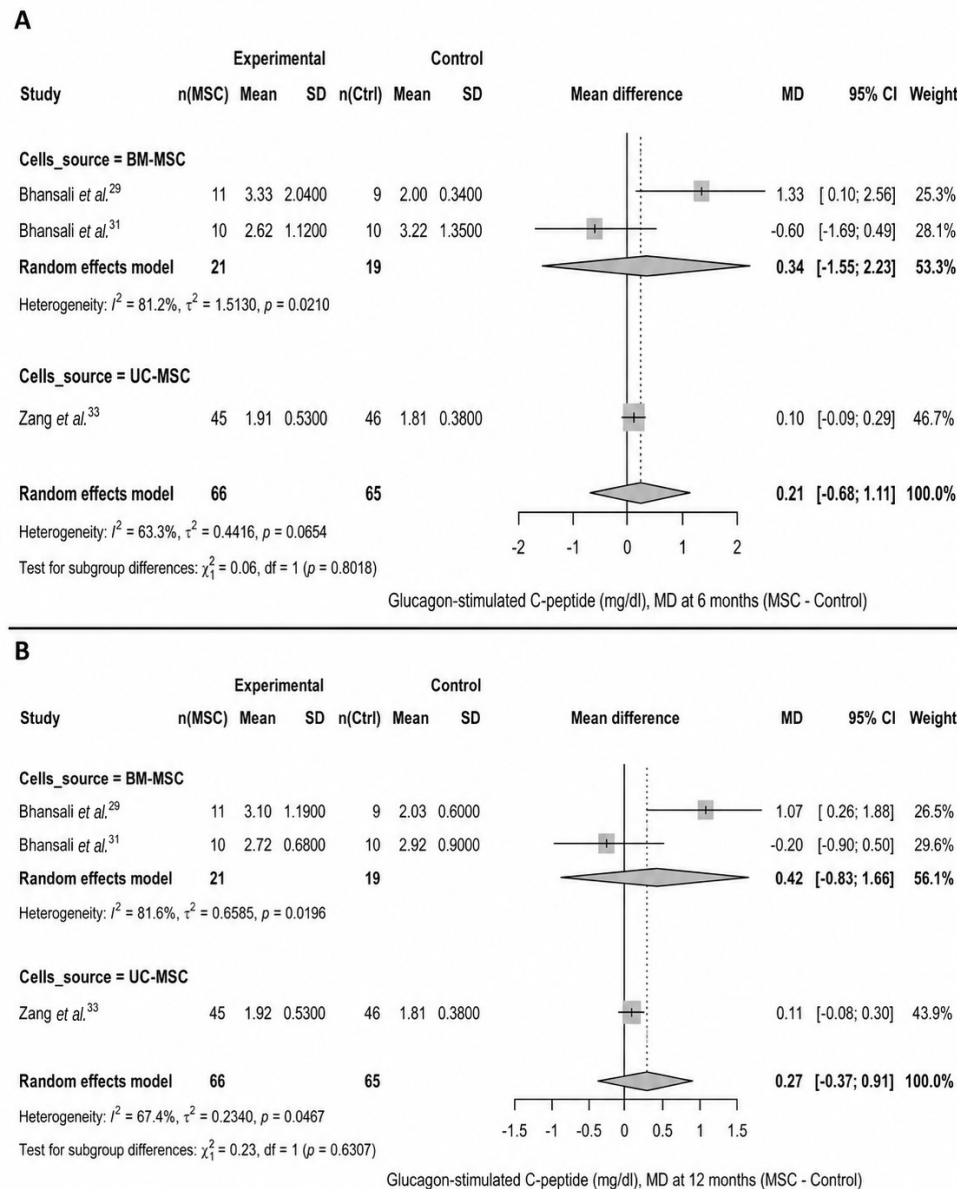


Figure 8. Primary analysis, glucagon-stimulated C-peptide assessment. (A) At 6 months. (B) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

MSC therapy improved HOMA-IR at 6 months but was not maintained at 12 months.

3.4. Measures of treatment efficacy (Secondary analysis)

3.4.1. Glycated hemoglobin assessment during follow-up

Across follow-up periods, pooled pre-post analysis

showed a significant reduction in HbA1c at all assessed time points, with effect estimates at 3 months (MD: -0.81 , 95% CI: -1.11 – -0.51), 6 months (MD: -1.02 , 95% CI: -1.81 – -0.22), and at 12 months (MD: -0.89 , 95% CI: -1.62 – -0.17). Considerable heterogeneity was observed throughout all timepoints ($I^2 = 96.2\%$, $p < 0.0001$; $I^2 = 97.1\%$, $p < 0.0001$; $I^2 = 96.4\%$, $p < 0.0001$, respectively). Subgroup analysis consistently demonstrated a significant subgroup difference favoring the UC-MSC subgroup at

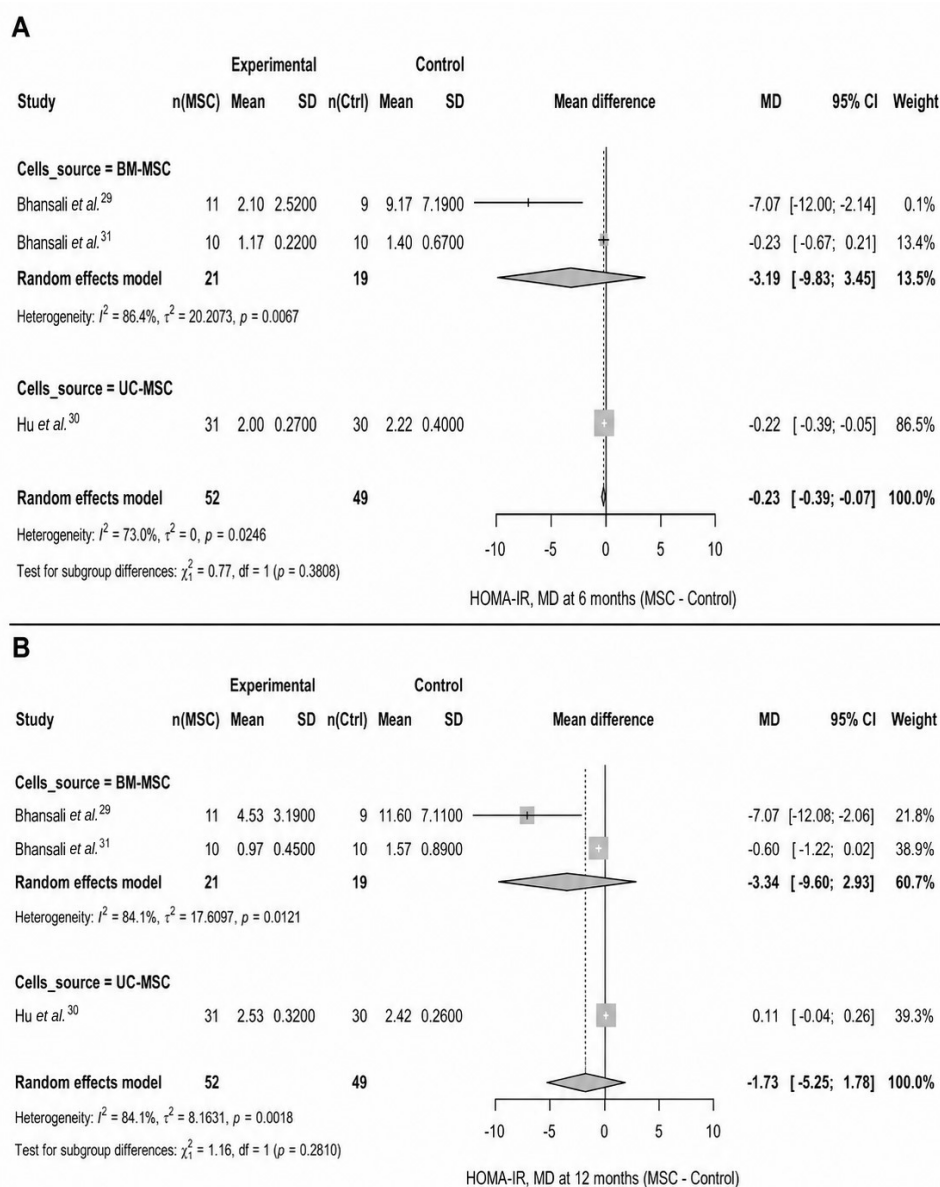


Figure 9. Primary analysis, HOMA-IR assessment. (A) At 6 months. (B) At 12 months.

Abbreviations: BM: Bone marrow; Ctrl: Control; CI: Confidence interval; df: Degree of freedom; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; MD: Mean difference; MSC: Mesenchymal stem cells; SD: Standard deviation; UC: Umbilical cord.

3 months ($\chi^2 = 16.61$, $p < 0.0001$), 6 months ($\chi^2 = 58.47$, $p < 0.0001$), and 12 months ($\chi^2 = 25.15$, $p < 0.0001$). Heterogeneity was lower in the BM-MSC subgroup at 3 months ($I^2 = 24.6\%$, $p = 0.2496$) than in the UC-MSC subgroup ($I^2 = 91.9\%$, $p < 0.0001$), absent in the BM-MSC subgroup at 6 months ($I^2 = 0\%$, $p = 0.5967$), with moderate heterogeneity in the UC-MSC subgroup ($I^2 = 67.7\%$, $p = 0.0452$). At 12 months, heterogeneity was significant in the BM-MSC subgroup ($I^2 = 80.1\%$, $p = 0.0249$) but low in the UC-MSC subgroup ($I^2 = 16.9\%$, $p = 0.3000$) (Figure 10A–10C). Overall, these findings indicate a sustained reduction in HbA1c over follow-up, with a consistently favorable effect in the UC-MSC subgroup.

3.4.2. Fasting blood glucose assessment during follow-up

Across the assessed follow-up periods, a pooled pre-post analysis of FBG showed a significant reduction at 3 months (MD: -19.05 , 95% CI: -36.33 – -1.76), but nonsignificant overall changes at 6 months (MD: -6.77 , 95% CI: -25.98 – 12.44) and 12 months (MD: -2.81 , 95% CI: -24.39 – 18.76). There was substantial heterogeneity at all time points ($I^2 = 96.1\%$, $p < 0.0001$; $I^2 = 96.0\%$, $p < 0.0001$; $I^2 = 97.2\%$, $p < 0.0001$, respectively). Despite the non-significant pooled effects at 6 and 12 months, subgroup analyses showed significant subgroup differences favoring the UC-MSC subgroup at 3 months ($\chi^2 = 77.19$, $p < 0.0001$), 6 months ($\chi^2 = 4.05$, $p = 0.0441$), and 12 months ($\chi^2 = 6.41$, $p = 0.0114$). No heterogeneity was observed in the BM-MSC subgroup at any of the three time points ($I^2 = 0\%$, $p = 0.4908$; $I^2 = 0\%$, $p = 0.4899$; $I^2 = 0\%$, $p = 0.4632$), while the UC-MSC subgroup showed no heterogeneity at 3 months ($I^2 = 0\%$, $p = 0.6375$) but considerable heterogeneity at 6 months ($I^2 = 91.4\%$, $p = 0.0007$) and 12 months ($I^2 = 91.2\%$, $p = 0.0008$) (Figure 11A–11C). Overall, these findings suggest that FBG improvement continued to favor UC-MSC across follow-up.

3.4.3. Fasting C-peptide assessment during follow-up

Across the evaluated follow-up timepoints, pooled pre-post analysis of FCP showed no significant overall change at 3 months (MD: 0.21 , 95% CI: -0.10 – 0.51), followed by an increase at 6 months (MD: 0.54 , 95% CI: 0.21 – 0.88) and a more modest increase at 12 months (MD: 0.41 , 95% CI: 0.00 – 0.83). There was considerable heterogeneity throughout ($I^2 = 90.4\%$, $p < 0.0001$; $I^2 = 94.5\%$, $p < 0.0001$; $I^2 = 96.0\%$, $p < 0.0001$, respectively). In contrast to HbA1c and FBG, subgroup analysis did not show a significant subgroup difference at 3 months ($\chi^2 = 0.11$, $p = 0.7448$), 6 months ($\chi^2 = 0.08$, $p = 0.7743$), or 12 months ($\chi^2 = 2.28$, $p = 0.1312$). At 3 months, heterogeneity was moderate in the BM-MSC subgroup ($I^2 = 69.5\%$, $p = 0.0704$) and

considerable in the UC-MSC subgroup ($I^2 = 93.8\%$, $p < 0.0001$). At 6 and 12 months, high heterogeneity remained evident within the UC-MSC subgroup ($I^2 = 96.2\%$, $p < 0.0001$, and $I^2 = 96.0\%$, $p < 0.0001$, respectively) (Figure 12A–12C). Overall, FCP tended to increase over time, but nonsignificantly between BM-MSC and UC-MSC subgroups.

3.4.4. Daily insulin requirement during follow-up

Across follow-up periods, pooled pre-post analysis showed a significant reduction in daily insulin requirement at all assessed time points. The pooled mean difference was MD: -20.22 (95% CI: -25.99 – -14.44) at 3 months, MD: -24.44 (95% CI: -31.43 – -17.45) at 6 months, and MD: -25.37 (95% CI: -31.55 – -19.19) at 12 months, with substantial heterogeneity throughout ($I^2 = 91.3\%$, $p < 0.0001$; $I^2 = 95.0\%$, $p < 0.0001$; $I^2 = 92.3\%$, $p < 0.0001$, respectively). However, subgroup analysis showed no significant subgroup difference at any time point: 3 months ($\chi^2 = 0.46$, $p = 0.4980$), 6 months ($\chi^2 = 0.44$, $p = 0.5089$), and 12 months ($\chi^2 = 0.00$, $p = 0.9898$). At 3 months, heterogeneity remained high within the BM-MSC subgroup ($I^2 = 93.5\%$, $p < 0.0001$). At 6 months, heterogeneity was lower in the BM-MSC subgroup ($I^2 = 28.9\%$, $p = 0.2357$) than in the UC-MSC subgroup ($I^2 = 97.0\%$, $p < 0.0001$). The same pattern was observed at 12 months, with lower heterogeneity in the BM-MSC subgroup ($I^2 = 50\%$, $p = 0.1574$) compared with the UC-MSC subgroup ($I^2 = 95.7\%$, $p < 0.0001$) (Figure 13A–13C). Overall, there was a sustained reduction in daily insulin requirement over follow-up, but with no significant difference between cell-source subgroups.

3.4.5. Homeostatic model assessment for insulin resistance during follow-up

Based on available 3-month data only, the pooled pre-post analysis of HOMA-IR yielded an overall estimate of MD: -0.51 (95% CI: -1.25 – 0.24), with considerable heterogeneity ($I^2 = 99.4\%$, $p < 0.0001$). However, subgroup analysis showed a significant heterogeneity ($\chi^2 = 359.07$, $p < 0.0001$), whereas the BM-MSC subgroup showed no heterogeneity ($I^2 = 0\%$, $p = 0.5779$) (Figure 14).

4. Discussion

This systematic review addresses a focused clinical question about T2DM and analyzes tissue-source-dependent benefits of MSC-based therapy. It provides temporally specific assessment of clinically relevant domains spanning 3–12 months of follow-up in T2DM patients, a chronic disease in which treatment sustenance is crucial. A significant feature of our study is the concomitant primary RCT-restricted comparative analysis and a supportive

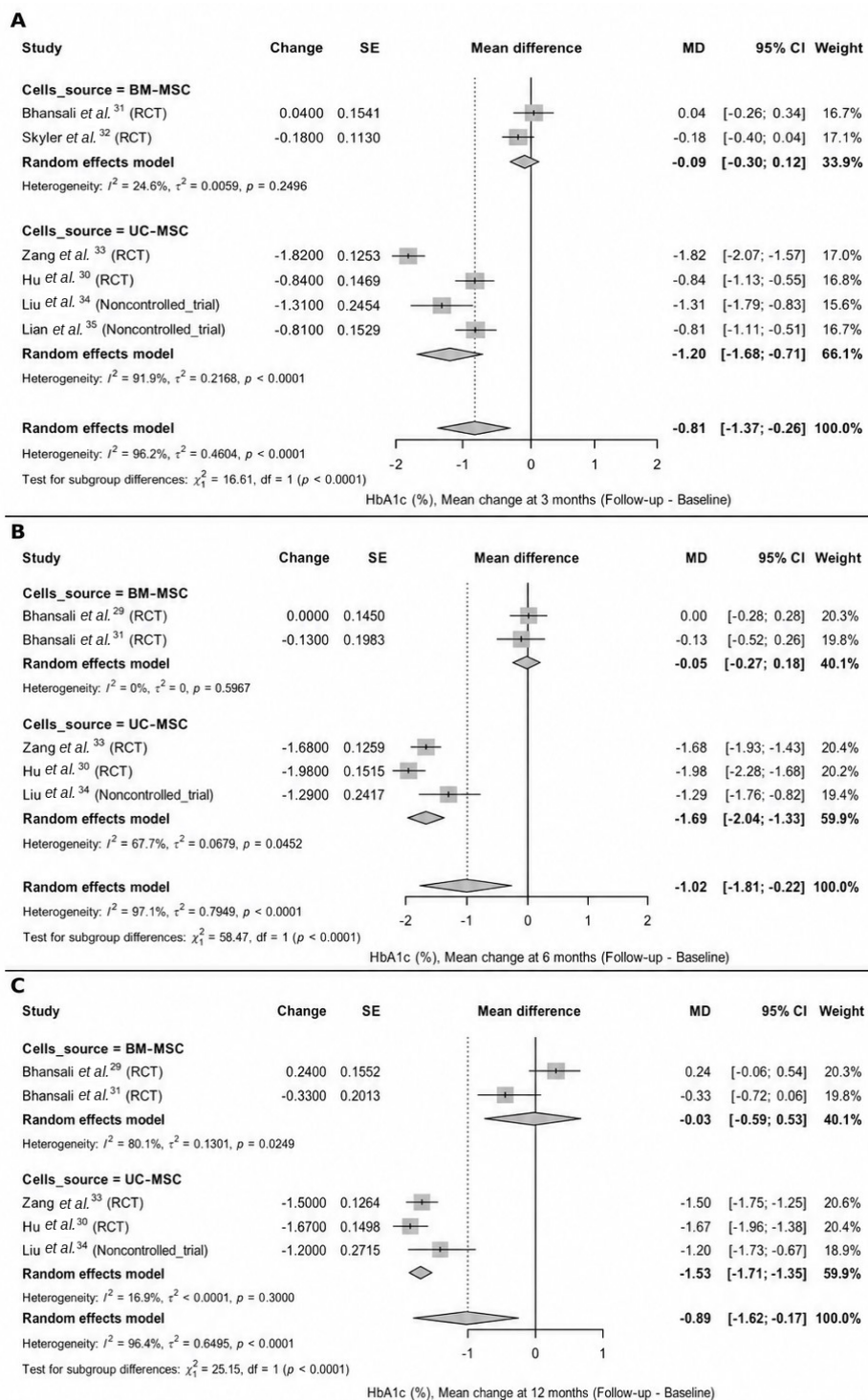


Figure 10. Secondary analysis, Hb1Ac assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SE: Standard error; UC: Umbilical cord.

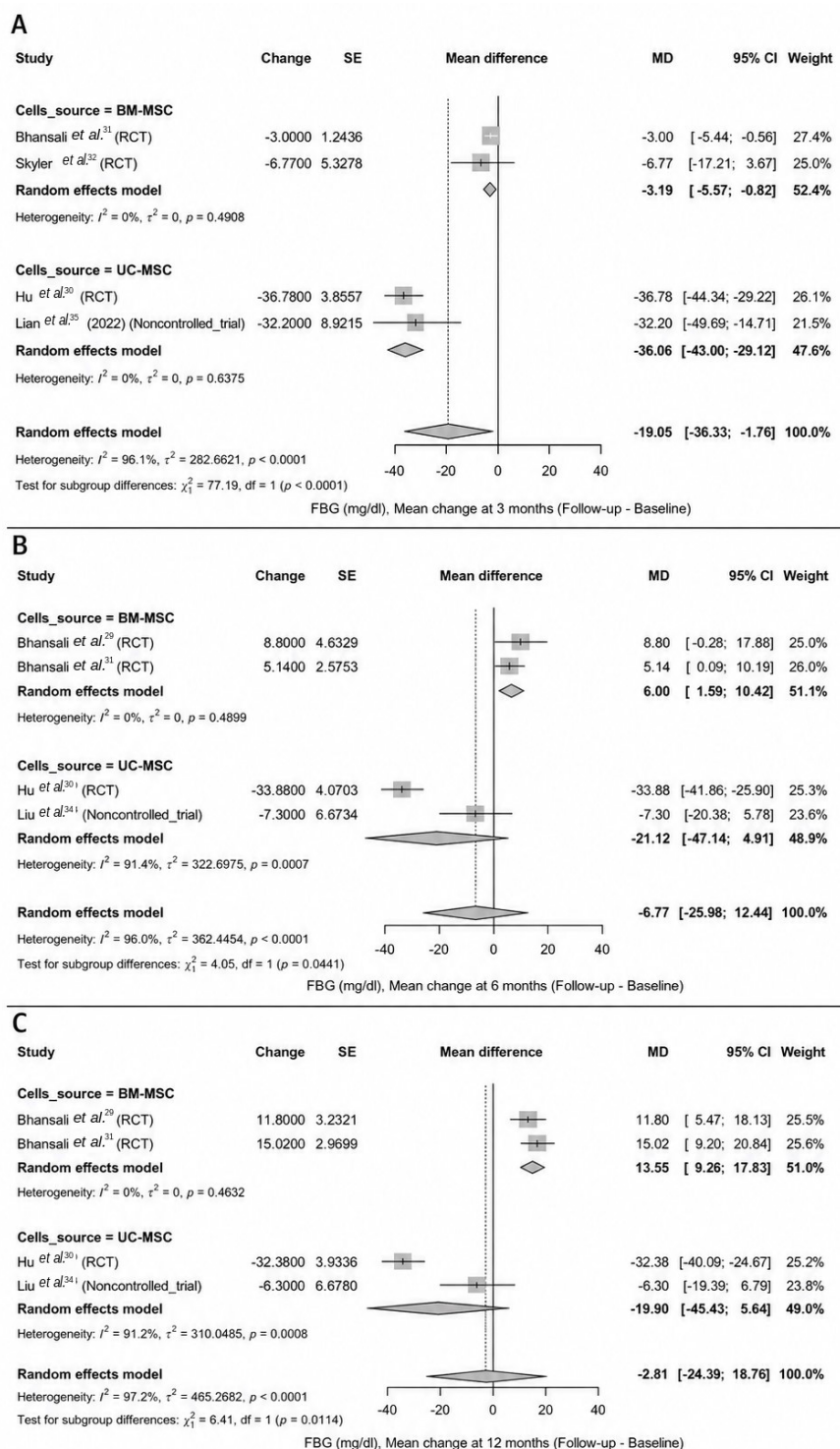


Figure 11. Secondary analysis, FBG assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; CI: Confidence interval; df: Degree of freedom; FBG: Fasting blood glucose; MD: Mean difference; MSC: Mesenchymal stem cells; SE: Standard error; UC: Umbilical cord.

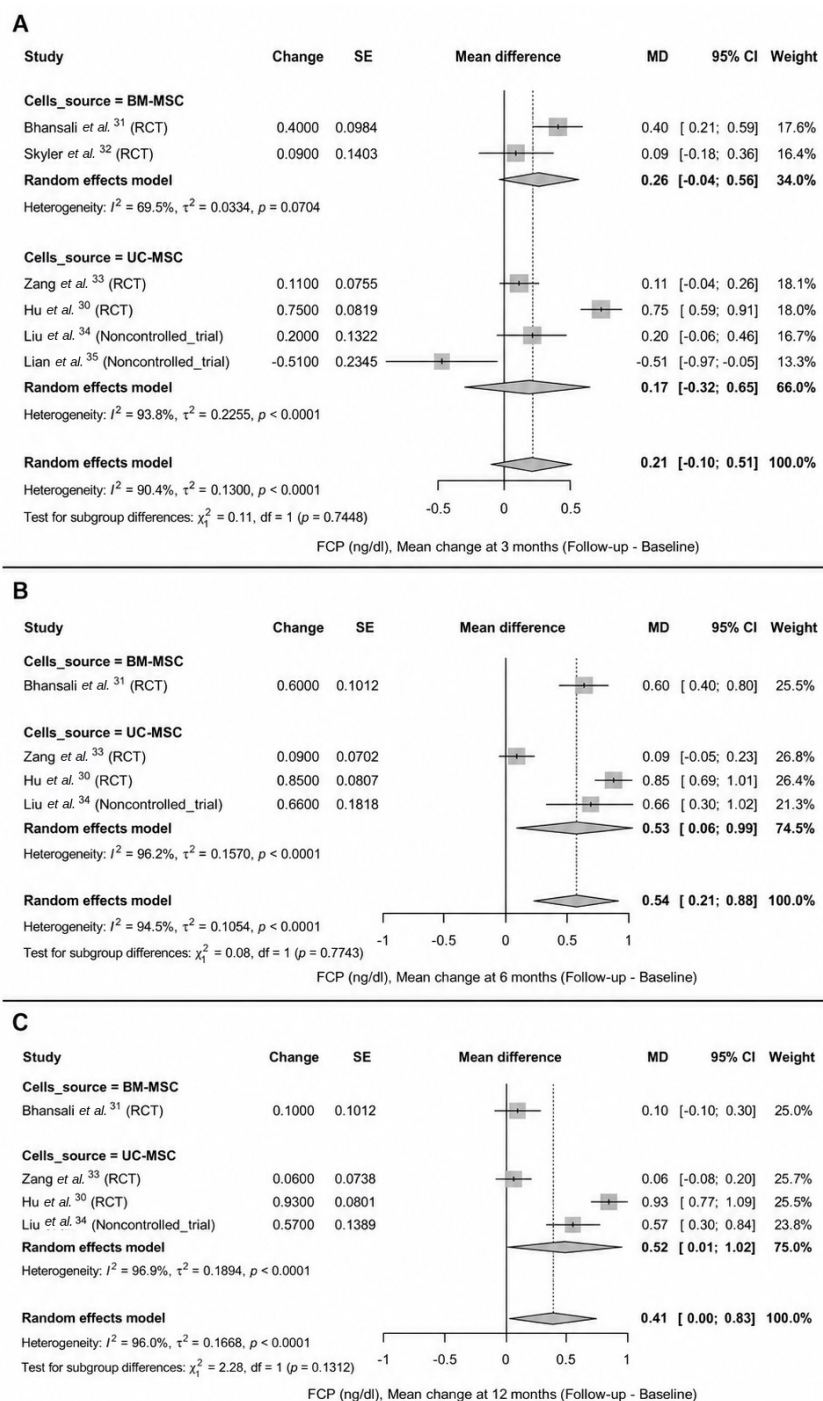


Figure 12. Secondary analysis, FCP assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; CI: Confidence interval; df: Degree of freedom; FCP: Fasting C-peptide; MD: Mean difference; MSC: Mesenchymal stem cells; SE: Standard error; UC: Umbilical cord.

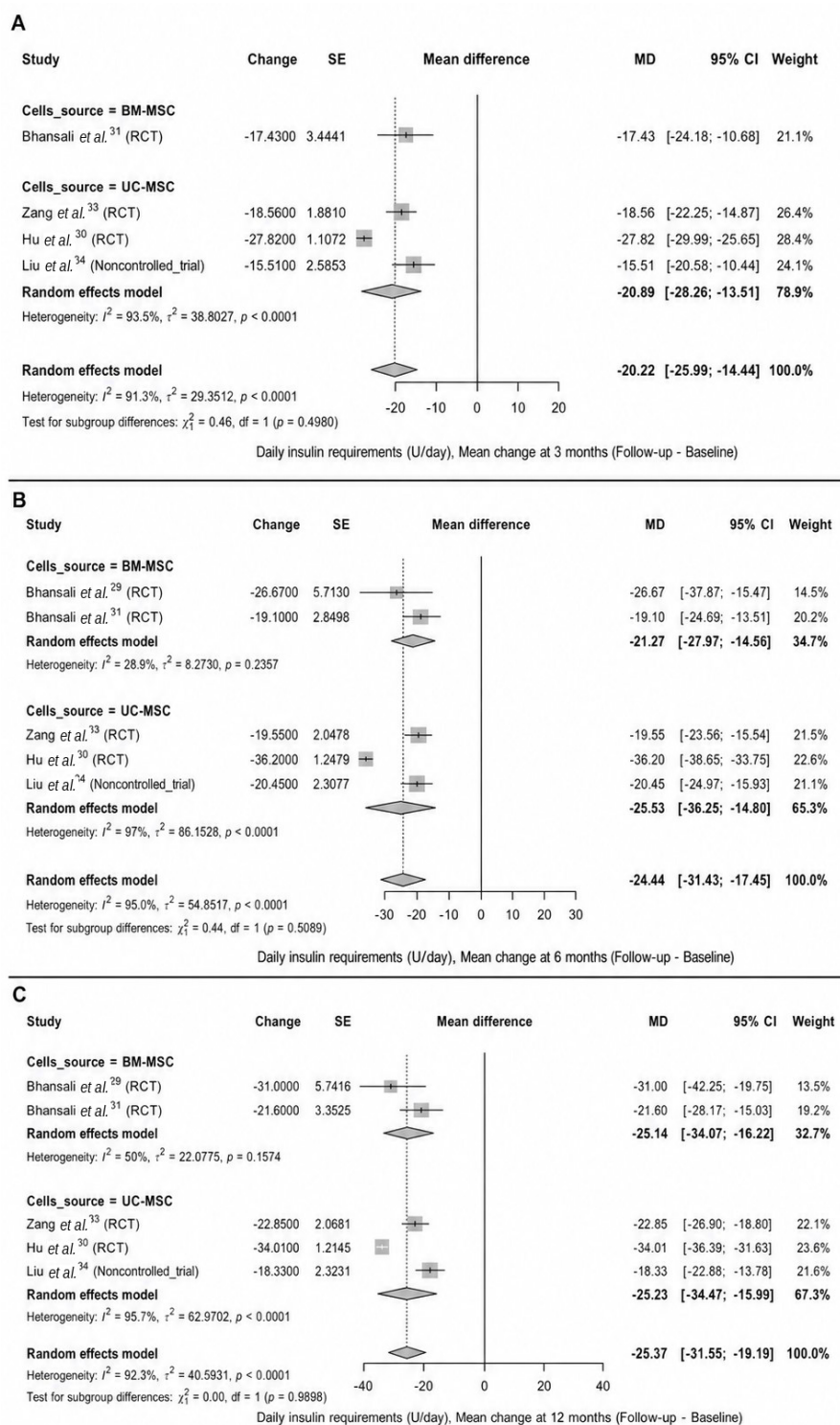


Figure 13. Secondary analysis, daily insulin requirements assessment. (A) At 3 months. (B) At 6 months. (C) At 12 months.

Abbreviations: BM: Bone marrow; CI: Confidence interval; df: Degree of freedom; MD: Mean difference; MSC: Mesenchymal stem cells; SE: Standard error; UC: Umbilical cord.

analysis based on baseline-to-post-treatment changes, to strengthen inference from the limited number of MSC-based Phase II/III clinical trials for T2DM, primarily assessing the effect of tissue source. The other salient findings of our study are: (i) UC-MSC showed a stronger glycemic effect, especially on HbA1c and FBG, which were sustained over 12 months of long-term follow-up; (ii) A sustained reduction in exogenous insulin requirements regardless of MSC tissue source; (iii) UC-MSCs exhibited greater efficacy than their counterparts.

In the primary (RCT-restricted) analysis, the subgroup analyses suggested stronger glycemic effects with UC-MSCs, particularly for HbA1c and FBG, although overall pooled effects versus control were often inconsistent. For example, at 12 months, subgroup differences between the two cell sources remained statistically significant for HbA1c and FBG, favoring UC-MSCs over 3 and 6 months of follow-up, thus indicating tissue-source-dependent sustained glycemic benefits. FCP also exhibited a tissue source-related pattern consistently favoring UC-MSCs across all three follow-up time points. Additionally, the glycemic benefits were linked with clinically meaningful reductions in exogenous insulin at all time points in the primary analysis, favoring UC-MSCs. In the secondary (supportive) analysis, pooling all eligible designs, a recurrent overall reduction in insulin requirements in favor of UC-MSCs was observed. Similarly, across the RCT-based comparative analyses, akin to the other domains, FCP showed a tissue-source-dependent pattern consistently favoring UC-MSCs; this directional advantage for UC-MSCs at early follow-ups became significant at the 12-week follow-up. Collectively, these findings suggested that UC-MSCs preserved or even modestly improved endogenous insulin secretory markers over time. However, the pooled effects are inconsistent and heterogeneous, requiring careful interpretation, for example, of HOMA-IR. The findings were inconsistent and heterogeneous across follow-up time points, making it difficult to infer a source-specific superiority. Given the reported tissue-source-related differences in the biology and functional characteristics of MSCs, such as doubling time, self-renewal capacity, migration capacity, senescence, immunomodulation, and paracrine behavior, these data may be biologically reasonable.³⁶ UC-MSCs may have more favorable biological properties, possibly due to a primitive cell population and a gene expression profile more similar to that of embryonic stem cells.^{37,38} Nonetheless, the observed heterogeneity and the limited number of trials per endpoint/time point indicate that the apparent advantage of UC-MSCs should be interpreted cautiously as suggestive rather than definitive superiority.

The existing systematic reviews and meta-analyses

broadly support a therapeutic usage of MSC-based interventions in diabetes. Most published literature has pooled heterogeneous patient populations (type 1 DM and T2DM), study designs (controlled and uncontrolled), delivery routes, and, importantly, different MSC sources, thereby obscuring tissue source-specific effects. A recent study reported significant within-group improvements (pre-post changes) in glycemic indices (HbA1c, fasting, and postprandial glucose), FCP, and insulin requirements.²³ However, their inter-group comparisons were less consistent at the end of follow-up. Notably, they observed a rise in FCP in T2DM after 12 months and a consistent reduction in insulin requirements among T2DM participants at 3, 6, and 12 months.²³ This pattern aligns with our findings that MSC-based therapy, regardless of cell source, may reduce the need for exogenous insulin. A more recent RCT-restricted study reported significant clinical improvement in insulin requirements, HbA1c, FCP, and postprandial blood glucose parameters after MSC-based therapy across follow-up periods of 3, 6, and 12 months, with subgroup analyses showing significant reductions in both type 1 DM and T2DM at 12 months.¹ At the same time, the study also highlighted that FCP at 6 months did not differ from placebo (overall and within subgroups), and that stimulated C-peptide remained comparable to placebo at 12 months.¹ This finding further supports the noted instability of β -cell function outcomes found in our review. Taken together, these findings align with our study's finding that MSC therapy, depending on the cell source, can primarily improve baseline insulin secretion and clinical glycemic control.

Two UC-MSCs-specific meta-analyses provided more supportive context for the directionality observed in UC-stratified results. Kassem and Kamal³⁹, focusing on Wharton's jelly-derived MSCs, reported improved insulin requirements, HbA1c, and FCP parameters after treatment compared with the control group. Likewise, Nada *et al.*⁴⁰ found that UC-MSC therapy significantly lowered HbA1c and reduced insulin requirements. Overall, their data largely aligns with our findings, indicating that MSC therapy is consistently associated with improvements in glycemic control. In addition, our observation that beta-cell function outcomes are less stable is supported by Kashbour *et al.*¹, who reported inconsistent effects of FCP at certain time points and no clear benefit for stimulated C-peptide versus placebo.

Despite the interesting findings, our study has limitations. Firstly, the number of RCTs included in the analysis is small, providing limited evidence, especially in subgroup analyses where some cell-source subgroups contained only one study. Such subgroup estimates reduce

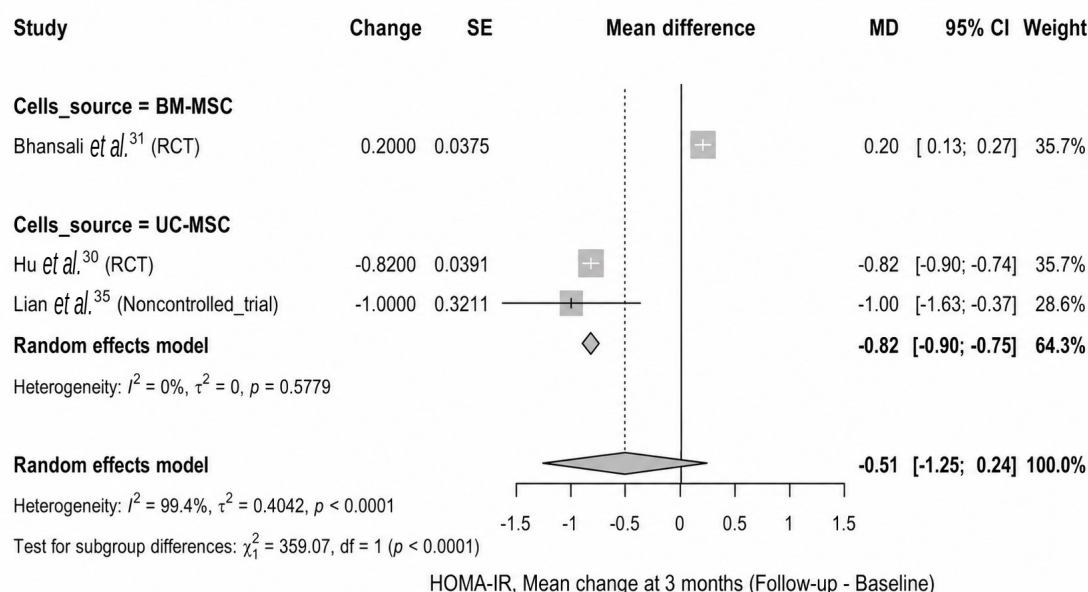


Figure 14. Secondary analysis, HOMA-IR assessment, at 3 months

Abbreviations: BM: Bone marrow; CI: Confidence interval; df: Degree of freedom; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; MD: Mean difference; MSC: Mesenchymal stem cells; SE: Standard error; UC: Umbilical cord.

precision and should not be interpreted as definitive comparative evidence. Secondly, some RCTs were at high risk of bias, while the non-randomized/self-controlled studies were inherently more susceptible to confounding and participant-selection bias, contributing to high heterogeneity. Because only a small number of trials were available for most outcomes and time points, exclusion-based sensitivity analyses were not performed, as they would have been underpowered and potentially misleading. Thirdly, extracting values from published graphs may introduce small measurement or rounding inaccuracies, although this approach was used only when numerical values were unavailable. Fourthly, variability in dose, route of administration, follow-up duration, and background diabetes care may have influenced the pooled estimates. In particular, reductions in insulin requirement may also be affected by changes in standard treatment, patient adherence, or clinical insulin titration during follow-up; therefore, this outcome should be interpreted cautiously, especially in supportive pre-post analyses. Lastly, formal publication-bias assessment and meta-regression were not performed due to the limited number of studies. Hence, these limitations warrant cautious interpretation of the data.

5. Conclusion

In conclusion, based on the currently available evidence

in the published literature, it is premature to infer that the tissue-source effect significantly impacts T2DM treatment outcomes. However, the observed pattern across 3- to 12-month follow-ups favors UC-MSCs, with better glycemic benefits and reduced dependence on exogenous insulin. Future high-powered studies comparing MSCs from different tissue sources are warranted.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

No datasets were generated or analyzed during the current study.

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