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Comparative efficacy of regenerative therapies for β-cell preservation in diabetes mellitus: A meta-analysis

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Abstract. Diabetes mellitus, which is associated with progressive loss of pancreatic β-cells, leading to insulin deficiency and hyperglycaemia, is of global health concern. Regenerative therapies, including stem cell therapies, have potential to address β-cell depletion and improve diabetes outcomes. The objective of this review was to compare the efficacy of stem cell-based regenerative therapies for the management of patients with both type 1 and type 2 diabetes mellitus. In carrying out this review, PubMed, ClinicalTrials.gov, and Google Scholar were the primary databases consulted. The analysis of 9 studies, including 5 randomised controlled trials and 4 non-randomised studies, revealed modest improvements in C-peptide levels, particularly in patients with type 2 diabetes mellitus, with a mean difference of 0.09 (95% confidence

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interval: -0.03, 0.21; p-value = 0.13), suggesting some benefit for β-cell preservation. However, the therapies did not show improvements in glycated haemoglobin levels, an increase in glycated haemoglobin level was observed, with a mean difference of 0.71 (95% confidence interval: 0.27, 1.15; p-value = 0.002), indicating worsening of glucose control, particularly in patients with type 2 diabetes mellitus. Although stem cell therapies show promise for β-cell preservation, such interventions do not appear to improve glycaemic control. This research has significant implications for clinicians involved in diabetes care, particularly those exploring regenerative treatments for type 1 and type 2 diabetes mellitus, and it underscores the necessity for personalised therapeutic strategies that account for the distinct pathophysiological mechanisms in these types of diabetes

Keywords: stem cell therapy; regenerative medicine; C-peptide levels; HbA1C levels; glycaemic control

Introduction

Diabetes mellitus (DM) is a global health challenge, largely due to the progressive loss of insulin-producing beta cells. Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are marked by beta-cell dysfunction, which contributes to chronic hyperglycaemia and severe complications. While current treatments focus primarily on managing blood glucose levels, these treatments do not address the underlying loss of beta cells. This limitation underscores the need for disease-modifying therapies, such as regenerative stem cell therapies, which aim to restore or preserve beta-cell function. The latest studies suggest that stem cell approaches, including mesenchymal stem cells (MSCs), show promise in regenerating beta cells and enhancing glycaemic control.

For example, as noted in the study by S.P. Chin *et al.* [1], umbilical cord mesenchymal stem cells, particularly those derived from umbilical cord blood, have shown promise in improving beta-cell function and glycaemic control, and it was concluded that it is safe for patients with T2DM and is associated with overall health outcomes, with improvement in metabolic indices such as liver and renal profile and systemic subclinical inflammation. Similarly, M. Izadi *et al.* [2] and S. Gao *et al.* [3] have noted the potential of MSCs to enhance endogenous beta-cell regeneration through the differentiation into insulin-producing cells or by supporting existing beta cells. In addition, in the study by T.W. Reichman *et al.* [4], islet-derived stem cells have been investigated for the role in beta-cell preservation and regeneration, and an increase in C-peptide levels (a marker of insulin secretion) in T1DM was reported. In a study by W. Wei *et al.* [5], bone marrow-derived mononuclear cells (BM-MNCs) were investigated for the ability to enhance beta-cell mass and improve glycaemic control in T2DM. The results demonstrated a significant reduction in Haemoglobin A1c (HbA1c) levels and improved insulin secretion in patients, suggesting that BM-MNC therapy may help restore beta-cell function by reducing inflammation and promoting beta-cell regeneration. This study highlighted the potential of BM-MNCs in addressing the metabolic dysfunction in T2DM, though challenges related to long-term efficacy and scalability remain.

Similarly, in a systematic review and meta-analysis conducted by I.G. Pires *et al.* [6], the clinical efficacy of stem cell therapies for T1DM and T2DM was assessed by comparing laboratory parameters, including fasting blood glucose, HbA1c, and C-peptide levels, before and after treatment. The study included 38 original articles with 647 control cases and 654 treated patients, with follow-up periods ranging from three to twelve months. The analysis revealed that stem cell therapies significantly reduced the need for insulin and improved fasting blood glucose and HbA1c levels in both T1DM and T2DM patients. Furthermore, a significant increase in C-peptide levels, a marker of beta-cell function, was observed in most patients. Notably, bone marrow-derived hematopoietic stem cell therapy produced better results compared to conventional treatments like semaglutide. Although the benefits were more pronounced in T1DM, stem cell therapies still showed potential in improving insulin resistance and metabolic parameters in T2DM patients, suggesting a promising avenue for further research and clinical application.

Despite the promising potential of stem cell therapies for managing diabetes, several challenges persist, particularly regarding immune rejection and long-term safety. D.B. Zuo *et al.* [7] emphasised that stem cell therapies have significant immunomodulatory capabilities, yet immune rejection remains a critical hurdle, especially in T1DM. MSCs have been shown to possess immune-regulatory properties that could counter autoimmune attacks against β-cells in T1DM. However, even with advancements such as CRISPR-edited human leukocyte antigen knockouts, the risk of immune rejection is not entirely mitigated, underscoring the need for more refined immune modulation techniques. In T2DM, which is often associated with insulin resistance and metabolic stress, stem cell therapies face additional challenges. M. Zarei *et al.* [8] highlighted the dual challenge of insulin resistance and β-cell dysfunction in T2DM, making it more difficult for regenerated β-cells to function optimally without addressing the metabolic underlying factors. The study noted that while stem cell therapies like MSCs can help rejuvenate pancreatic function, the effectiveness is limited unless these metabolic stressors are concurrently managed. This supports the need for combination therapies that integrate stem cell-based interventions with lifestyle modifications or pharmacological treatments aimed at reducing insulin resistance.

Further studies by A.M. Mouzzam *et al.* [9] revealed that stem cell therapies hold significant potential in reversing T1DM by regenerating insulin-producing β-cells. However, the authors also pointed out that immune rejection

remains a significant barrier, as even autologous stem cell treatments may not prevent the autoimmune destruction of newly created β-cells. The study thus emphasised the importance of developing personalised therapies tailored to the immunological profiles of individual patients. This would help improve the success rates of these therapies and avoid the issue of immune rejection. In addressing the challenges of long-term safety and scalability, B. Gieroba *et al.* [10] discussed the potential complications of stem cell therapies, including tumorigenicity and the difficulty of ensuring consistent outcomes across diverse patient populations. The study focused on the clinical challenges of translating stem cell-based treatments into large-scale applications. Thereby suggesting that overcoming these barriers may require advancements in stem cell engineering, such as the use of encapsulation technologies or the development of more controlled differentiation protocols to prevent the formation of unwanted cell types, such as those contributing to tumours.

Additionally, S.M. Nameghi [11] emphasised the need for personalised approaches to stem cell therapies, and the findings from the research demonstrated that targeting the unique metabolic and immunological challenges in each patient, especially those with T2DM, is crucial for improving the efficacy of stem cell treatments. Personalised medicine could be integrated with stem cell therapies to account for individual genetic predispositions and responses to metabolic stress, thereby enhancing the therapeutic outcomes and minimising adverse effects. Finally, A. Hassanein & S. Akhtar [12] explored the challenges related to scalability and the complex nature of diabetes management, stressing that while stem cell therapies show promise, there is still a lack of sufficient comparative studies that evaluate the long-term effects of these therapies across various patient groups. The researchers argued that future research should focus on conducting large-scale, long-term clinical trials that assess both the efficacy and safety of stem cell-based interventions in diverse patient populations to improve clinical decision-making and direct future funding toward promising areas.

Based on this, the present review aimed to compare the efficacy of the adoption of regenerative therapies (stem cell therapies) for the preservation of β-cells in T1DM and T2DM by considering C-peptide levels and HbA1c levels as outcome measures.

Materials and Methods

This study followed the guidelines for meta-analysis outlined in the analysis by M.J. Page *et al.* [13]. To address the goal, the PICO framework was employed [14]. The Population (P) for this study included human patients diagnosed with T1DM or T2DM. The Intervention (I) was regenerative therapy through stem cell approaches. The Comparison (C) was made between patients receiving stem cell therapy and untreated patients or those receiving conventional treatments. The Outcome (O) variables of interest were C-peptide levels, HbA1c, insulin requirements, and fasting plasma glucose levels. The inclusion criteria considered were original research articles, including randomised controlled trials and non-randomised studies, published in English between 2020 and 2025 that involved human subjects, specifically individuals diagnosed with T1DM or T2DM. The therapy under investigation had to be stem cell-based. Furthermore, to be eligible, studies needed to report on either HbA1c levels or C-peptide. The excluded studies were those that were not published in English, those involving animal subjects, reviews, conference proceedings, or those where full-text access was unavailable. A comprehensive search was carried out in PubMed, ClinicalTrials.gov, and Google Scholar from 30 November 2025 to 3 December 2025. In searching the databases, a combination of keywords relating to diabetes mellitus, such as diabetes mellitus, hyperglycaemia, and those relating to stem cell therapies were employed. The search results were refined with the application of Boolean operators "AND" and "OR" [15]. MeSH terms were also applied in searching PubMed, which is the only database that features such terms [16]. The compiled search terms and filters applied for each database (such as year of publication, English language, and human participants) were represented in Table 1.

Table 1. Studies search strategy

Database	Search term	Search yield	Filters applied	Yield following application of filters
ClinicalTrials.gov	(diabetes mellitus OR hyperglycaemia) AND (C-peptide Levels OR HbA1c Levels) AND (stem cells OR progenitor cells OR hematopoietic stem cells OR bone marrow-hematopoietic stem cells OR mesenchymal stem cells OR bone marrow-mesenchymal stem cells OR bone marrow mononuclear cells OR umbilical cord blood OR umbilical cord-mesenchymal stem cells OR placenta-derived mesenchymal stem cells OR insulin-secreting-adipose-derived mesenchymal stem cells)	89	nil	
Google Scholar	(diabetes mellitus OR hyperglycaemia) AND (stem cells OR progenitor cells OR hematopoietic stem cells OR bone marrow-hematopoietic stem cells OR mesenchymal stem cells OR bone marrow-mesenchymal stem cells OR bone marrow mononuclear cells OR umbilical cord blood OR umbilical cord-mesenchymal stem cells OR placenta-derived mesenchymal stem cells OR insulin-secreting adipose-derived mesenchymal stem cells)	204	2020-2025	69

Continued Table 1

Database	Search term	Search yield	Filters applied	Yield following application of filters
PubMed	("diabetes mellitus"[Title/Abstract] OR "hyperglycaemia"[Title/Abstract]) AND ("stem cells"[Title/Abstract] OR "progenitor cells"[Title/Abstract] OR "hematopoietic stem cells"[Title/Abstract] OR "bone marrow hematopoietic stem cells"[Title/Abstract] OR "mesenchymal stem cells"[Title/Abstract] OR "bone marrow mesenchymal stem cells"[Title/Abstract] OR "bone marrow mononuclear cells"[Title/Abstract] OR "umbilical cord blood"[Title/Abstract] OR "umbilical cord mesenchymal stem cells"[Title/Abstract] OR "placenta derived mesenchymal stem cells"[Title/Abstract] OR (("insulin"[Supplementary Concept] OR "insulin"[All Fields] OR "insulin"[MeSH Terms] OR "insulin s"[All Fields] OR "insuline"[All Fields] OR "insulinic"[All Fields] OR "insulinisation"[All Fields] OR "insulinised"[All Fields] OR "insulins"[MeSH Terms] OR "insulins"[All Fields]) AND "derived mesenchymal stem cells"[Title/Abstract]))	3,044	2020-2025, Free full text, Clinical Trial, Multicentre Study, Observational Study, Randomised Controlled Trial, English, Humans	16

Source: compiled by the authors

Following a systematic search in PubMed, Google Scholar, and ClinicalTrials.gov, 3,403 records were retrieved. After applying appropriate filters, 240 articles remained, then 8 duplicates were removed, 177 were removed during title and abstract screening, and the full text of 12 articles was not retrieved. The full text of the remaining 43 articles was subjected to a detailed eligibility assessment, after which 34 articles were excluded that did not meet the inclusion criteria, and the remaining 9 articles were included in the analysis in this review. The literature selection process was illustrated in the PRISMA flow diagram, as shown in Figure 1.

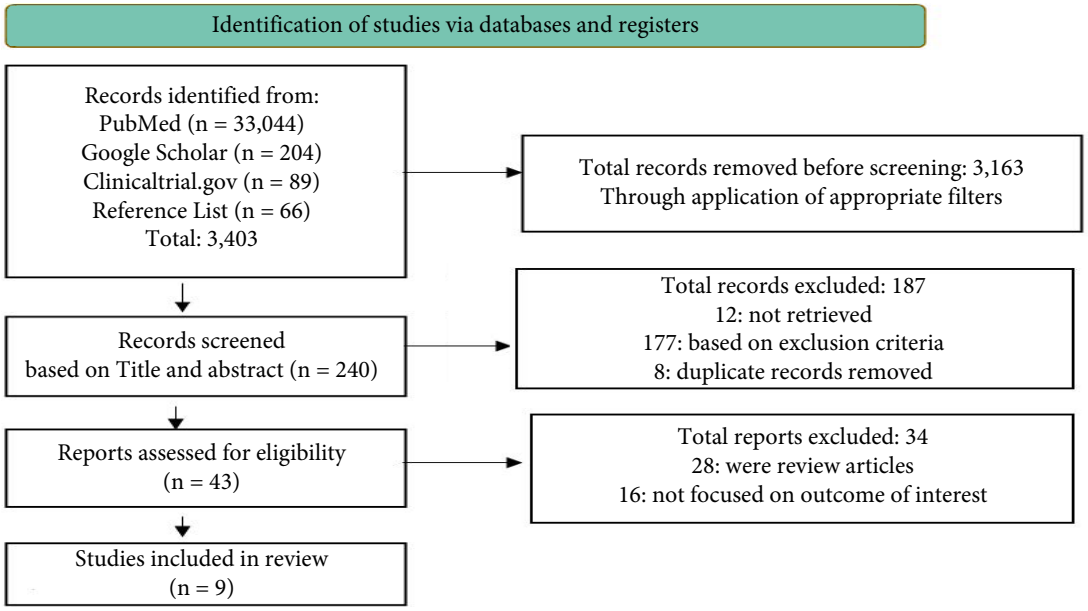

Figure 1. PRISMA flow diagram

Source: compiled by the authors

After retrieving the relevant studies, the data extraction was conducted independently by two researchers, and discrepancies were resolved through discussion. Key data extracted from the studies included information relating to study details, patient demographics, regimen, and laboratory parameters for diabetes (HbA1c and C-peptide) at baseline and during the follow-up period. To assess the quality of the included studies, the Revised Cochrane risk-of-bias tool for randomised trials Version 22 was employed for the randomised controlled trials [17] and the ROBINS-I tool for non-randomised studies [18]. The included studies in this review comprised a total of 9 studies, of which 5 were randomised controlled trials, and 4 were non-randomised studies, with 3 focusing on T1DM, 7 on T2DM, and 3 out of the 9 studies did not feature a control group. The included studies were conducted

in different countries of the world, including China (5), Iran (2), Sweden (1), and Malaysia (1). A total of 694 participants were featured in all the studies; the mean age of patients varied from 10.27 years to 61.5 years, with T1DM patients typically younger than T2DM patients. However, there was a significant difference in the duration of the disease before therapy. The T1DM patients had shorter histories compared to those with T2DM; this is due to the distinct characteristics of both conditions. All regimens involved stem cell therapies administered at varying doses, ranging from 1×10^6 to 200 million cells per dose. The mode of administration recorded was intravenous (IV) and intra-arterial pancreatic infusion (IAPI). Follow-up periods varied, with the majority of studies reporting 12 months, although some extended to as long as 96 months. This variation in study characteristics underscores the diverse approaches used to assess regenerative therapies and the potential for β-cell preservation in diabetes. Table 2 summarised the characteristics of the included studies in this review. Thus, this review analysed 9 studies (5 randomised controlled trials (RCT), 4 non-randomised) involving 710 participants with T1DM and T2DM, evaluating stem cell therapies with varying doses, administration routes, and follow-up periods.

Table 2. Characteristics of included studies

Study	Country	Study design	Type of DM	Number of patients TG / CG	Mean age of participants (years)	History of disease	Regimen	Mean regimen dose	Mode of injection	Mean follow-up (months)
M. Izadi *et al.* [2]	IR	RCT	T1DM	TG = 11; CG = 10	TG=10.27 CG=11.5	Newly diagnosed (<6 weeks)	BM-MSCs	1×10^6 cells/kg	IV	12
P.O. Carlsson *et al.* [19]	SE	RCT	T1DM	TG = 9; CG = 5	TG=31 CG=31	Newly diagnosed (<2 years)	UC-MSCs	200 mln cells	IV	12
Z. Wu *et al.* [20]	CN	RCT	T2DM	57(29 in MSC + MC and 28 in MC-only group)/ 29 in CG)	Dual MSC + MC group = 52.8; MC-only group = 53.2; CG = 54.6	≥ 3 and ≤ 15 years	MSC and MC	1×10^6 cells/kg	IV and IAPI	96
L. Zang *et al.* [21]	CN	RCT	T2DM	TG = 45; CG = 46	TG = 50; CG = 50.45	< 20 years	UC-MSCs	1×10^6 cells/kg	IV	12
L. Zang *et al.* [22]	CN	RCT	T2DM	TG = 37; CG = 36	TG = 50.97; CG = 50.53	< 20 years	UC-MSCs	1×10^6 cells/kg	IV Infusion	12
S.P. Chin *et al.* [1]	MS	ROS	T2DM	218 in 6 mo. FUG and 83 in 12 mo. FUG, no CG	61.5	Not reported	UC-MSCs	$50–100\times10^6$	IV Infusion	6 in 6 FUG and 12 in 12 FUG
J. Lu *et al.* [23]	CN	Open-label, parallel-arm, non-randomised prospective study	T1DM	TG=27; CG=26	TG=22.4; CG=27.4	Not reported	UC-MSCs	1×10^6 cells/kg	IV Infusion	12
R. Raoufinia *et al.* [24]	IR	Open-label, single-arm pilot clinical trial	T2DM	11 participants; no CG	20-65	≥ 10 years	UC-MSCs	1×10^8 cells/kg	IV Infusion	2
X.F. Lian *et al.* [25]	CN	Single-arm, open-label, exploratory clinical trial	T2DM	16 participants; no CG	52.5	10.06 ± 5.74 years	UC-MSCs	1×10^6 cells/kg	IV Infusion	3

Note: BM-MSCs – bone marrow-mesenchymal stem cells, UC-MSCs – umbilical cord-mesenchymal stem cells, MC – mononuclear stem cell; TG – Treatment Group; CG – Control Group; FUG – Follow-Up Group; ROS – Retrospective observational study; IR – Iran; SE – Sweden; CN – China; MS – Malaysia
Source: compiled by the authors

Based on the quality assessment of the included studies, among the five randomised controlled trials, the majority demonstrated low risk of bias across most domains except for M. Izadi *et al.* [2], where concerns regarding missing outcome data were noted due to participant dropout, which could influence the robustness of the findings. For the four non-randomised studies, moderate risks were identified in the works by S.P. Chin *et al.* [1], J. Lu *et al.* [23] and R. Raoufinia *et al.* [24], due to potential confounding factors and unclear adjustments, which could lead to over- or underestimation of the treatment effects. These biases, particularly related to missing data and confounding, may lead to misleading conclusions, potentially exaggerating the efficacy of stem cell therapies in β-cell preservation or misrepresenting the true impact of these therapies on diabetes management.

The software used for the meta-analysis was Review Manager version 5.4.1. The effect estimates from the included studies were pooled by adopting a random-effects model, inverse variance, and mean difference (MD) of C-peptide and HbA1C levels at baseline and after therapy were used for comparison. The use of random-effects modelling in this analysis is beneficial in that it accounts for heterogeneity among studies. Analyses of subgroups were carried out according to the type of stem cell therapy and the type of diabetes. To test the robustness of the finding, sensitivity analyses were conducted by excluding one study at a time in the analysis to observe the effect on the overall pooled estimate. This specific type of sensitivity analysis was conducted to assess whether the exclusion of any single study would significantly alter the pooled results. However, several limitations must be considered when interpreting the results from this study. The significant heterogeneity across studies, particularly in terms of the stem cell types used, dosage, administration routes, and follow-up durations, may have contributed to the variability in outcomes. Additionally, the relatively small sample sizes and short follow-up periods in many of the included studies limit the generalisability of the findings. Moreover, while this meta-analysis provides a pooled estimate of the effects of stem cell therapies on C-peptide and HbA1c levels, it does not account for other important factors such as quality of life, adverse events, and cost-effectiveness, which are critical for evaluating the feasibility of widespread clinical implementation.

Results and Discussion

C-peptide levels are closely linked to β-cell preservation in diabetes. C-peptide, an insulin byproduct, is a biomarker for β-cell activity. Research indicates that higher C-peptide levels enhance β-cell function and reduce diabetes complications [26]. Conversely, low C-peptide levels cause glucose fluctuations, acute hypoglycaemia, and HbA1c. According to previous studies, C-peptide levels predict β-cell function in T2DM. Therefore, C-peptide levels serve as a measure of the effectiveness of treatments aimed at maintaining β-cell activity in diabetes management [27]. For T1DM, as shown in Figure 2, the pooled effect size across studies showed a mean difference (MD) of 0.04 (95% CI: -0.09, 0.18). The p-value associated with this effect is 0.51, which indicates that the observed minimal improvement in C-peptide levels is not statistically significant. This suggests that stem cell therapies, while showing a slight trend towards increasing C-peptide levels, do not provide strong enough evidence to support a meaningful impact on β-cell function in T1DM. The subgroup analysis for different types of stem cells, such as BM-MSC and UC-MSC, also did not reveal significant heterogeneity, reinforcing the conclusion that the impact of stem cell therapies on C-peptide levels in T1DM is inconclusive.

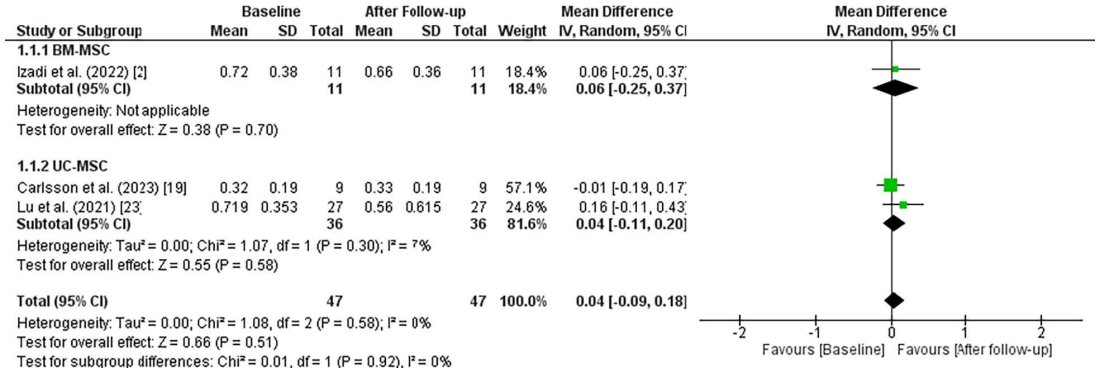

Figure 2. Forest plot for fasting C-peptide levels (ng/mL) in T1DM individuals from baseline to follow-up
Source: created by the authors

In contrast, the results for T2DM, as shown in Figure 3, presented more favourable insights. The pooled effect for T2DM across studies showed a mean difference (MD) of 0.09 (95% CI: -0.03, 0.21). The p-value for this pooled effect is 0.13, indicating a non-significant, modest improvement in C-peptide levels following stem cell therapy. This suggests that stem cell therapies are more effective in enhancing β-cell regeneration or function in T2DM patients compared to T1DM. Subgroup analysis for T2DM, including therapies such as BM-MSC+MC, MC, and UC-MSCs, demonstrated some variability in outcomes, but the overall trend points toward a positive effect on C-peptide levels, though the effect remains modest.

When comparing the pooled effects for T1DM and T2DM, it is evident that stem cell therapies yield more consistent but modest effects in T2DM patients. The p-value of 0.13 for T2DM suggests a more pronounced effect compared to the p-value of 0.51 for T1DM, highlighting the more substantial response to stem cell therapies in T2DM. This difference may be attributed to the distinct pathophysiological mechanisms of β-cell loss in both types of diabetes. T1DM, characterised by autoimmune-mediated destruction of β-cells, presents more challenges for regeneration, whereas T2DM, driven by metabolic stress, may be more responsive to therapies targeting the rejuvenation of existing β-cells. While both T1DM and T2DM show some potential for improvement in C-peptide levels with stem cell therapies, the effects are more pronounced in T2DM. This highlights the need for personalised regenerative approaches tailored to the specific pathophysiological mechanisms

of β-cell dysfunction in each form of diabetes. Further research with larger sample sizes and standardised protocols is needed to fully evaluate the long-term efficacy and safety of stem cell-based therapies for β-cell preservation.

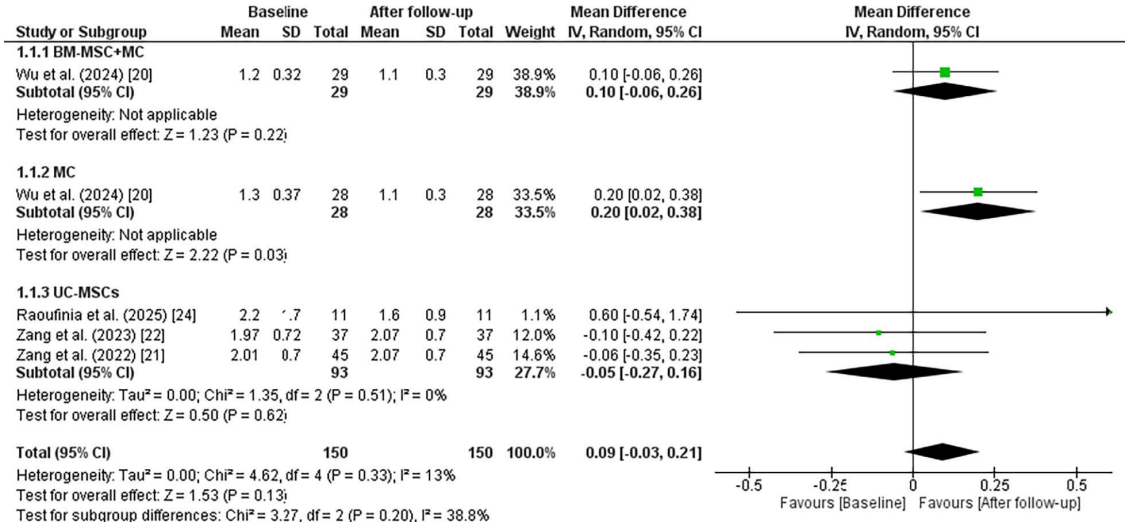

Figure 3. Forest plot for fasting C-peptide levels (ng/mL) in T2DM individuals from baseline to follow-up
Source: created by the authors

HbA1c levels significantly affect β-cell preservation in diabetes. Insulin production decreases with low β-cell activity, leading to hyperglycaemia and high HbA1c levels. Research links high HbA1c levels to impaired β-cell function and diabetes consequences. Conversely, lower HbA1c levels improve β-cell function and glycaemic control. Monitoring HbA1c levels can indicate β-cell function and the effectiveness of therapies to maintain it. Maintaining β-cell activity is crucial for diabetes management, and HbA1c readings can assess treatment effectiveness [28, 29].

For T1DM, according to Figure 4, the total pooled effect across studies showed a mean difference (MD) of 0.78 (95% CI: -0.32, 1.89), with a p-value of 0.16. This indicates that stem cell therapies investigated have a non-significant increase in HbA1c levels, suggesting a potential worsening of glucose control. The wide confidence interval (CI) and the high p-value suggest that any change in HbA1c is modest and likely due to random variation. The subgroup analysis for BM-MSC and UC-MSC therapies revealed some variability in the outcomes, but overall, the results do not support a clear, consistent benefit of stem cell therapies in lowering HbA1c in T1DM patients.

In contrast, the results for T2DM in Figure 5 showed a statistically significant increase in HbA1c levels, with a mean difference (MD) of 0.71 (95% CI: 0.27, 1.15) and a p-value of 0.002. This suggests that stem cell therapies are associated with a worsening of glucose control in T2DM patients, contrary to the expected outcome (i.e., a worsening of glucose control in T2DM patients rather than improvement). The subgroup analysis showed variability in outcomes with effect size in the MC group, derived from Z. Wu *et al.* [20] showing -0.10, which indicates a decrease in HbA1c levels, which is not statistically significant. However, the overall result indicates a need for further investigation into the effects of stem cell therapies on HbA1c levels in T2DM.

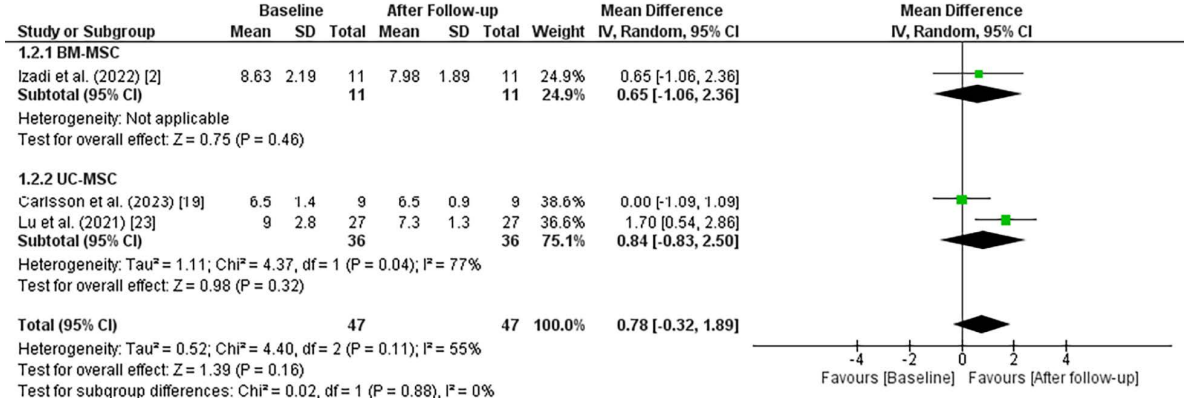

Figure 4. Forest plot for HbA1c levels (%) in T1DM individuals from baseline to follow-up
Source: created by the authors

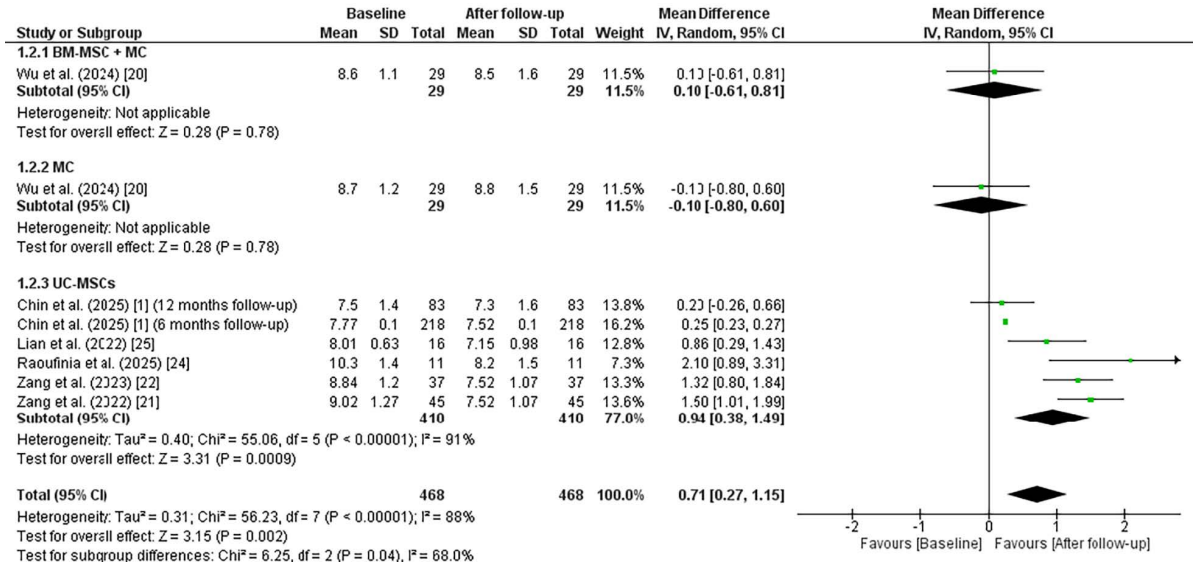

Figure 5. Forest plot for HbA1c levels (%) in T2DM individuals from baseline to follow-up
Source: created by the authors

Therefore, in T1DM, stem cell therapies showed no significant effect on HbA1c levels, indicating only modest changes that are likely due to random variation. For T2DM, stem cell therapies were associated with a significant increase in HbA1c, suggesting a potential worsening of glucose control, and further research is needed to better understand these effects. The findings of this study provide insights into the efficacy of stem cell therapies in preserving β-cell function in T1DM and T2DM. The results indicated that in terms of C-peptide levels, stem cell therapies have limited benefits in T1DM compared to T2DM, with minimal improvement in C-peptide levels, indicating some benefit in β-cell preservation. On the other hand, a non-significant increase in HbA1c levels was observed in T1DM, and a significant increase in HbA1c levels was observed in T2DM, suggesting a potential worsening of glucose control. These findings suggest that stem cell therapies may offer a modest benefit in preserving β-cell function due to an increase in c-peptide levels, particularly in T2DM patients, but do not appear to have a beneficial impact on HbA1c levels in either T1DM or T2DM.

The use of stem cell-based therapies, particularly MSCs, for diabetes management has been explored in various meta-analysis studies. For example, Q. Wu *et al.* [30] conducted a meta-analysis on the efficacy of stem cell transplantation for T1DM and found that MSC therapy could reduce insulin requirements and improve C-peptide levels, although the improvement was not statistically significant. This is consistent with the results of the current study, which observed a slight improvement in C-peptide levels in patients with T1DM, which is also not statistically significant. However, in contrast, Q. Wu *et al.* found that MSC therapy significantly decreased HbA1c levels, whereas in this study, an increase in HbA1c levels was recorded. This decrease in HbA1c was also reported in the study by J. He *et al.* [31], in which MSC therapy was also investigated, and according to the report for fasting C-peptide levels, no significant increase in fasting C-peptide levels was recorded as well. Similarly, S.Y. Sun *et al.* [32] reported a significant improvement in C-peptide levels in T1DM patients following MSC therapy, supporting the idea that stem cells may help regenerate insulin-producing β-cells. However, S.Y. Sun *et al.* also reported a significant decrease in HbA1c levels in RCTs, but with high heterogeneity. This suggests that while there may be some improvement in glycaemic control, it is not consistent across all studies, and the effect size is uncertain. Moreover, according to findings of M. Kashbour *et al.* [33], significant reductions in HbA1c levels in T2DM patients treated with MSCs were also reported.

A potential explanation for the variation in HbA1c level outcomes recorded in studies such as those of Q. Wu *et al.* [30], J. He *et al.* [31], and S.Y. Sun *et al.* [32] compared with the findings in this study may be attributed to differences in sample sizes, cell source, and injection protocols across studies as well as the comparator arms included in the meta-analysis. In addition, it is worth noting that in these studies, comparisons were made between treatment groups and control groups, whereas in this study, comparison was made with baseline outcomes in treatment groups and the outcomes in treatment groups recorded at the end of varying follow-up periods across studies. Moreover, changes in HbA1c did not consistently align with modest changes in fasting C-peptide, suggesting that β-cell preservation may not translate directly into improved glycaemic control [34].

Nevertheless, a critical consideration in interpreting findings is the differences in pathophysiology between T1DM and T2DM, which likely contribute to the varied responses observed in stem cell therapies. T1DM is characterised by autoimmune destruction of β-cells, so it is essential to manage the immune system to avoid the

rejection of newly transplanted or regenerated β-cells, as the autoimmune destruction of these cells is the primary factor contributing to this condition. It is essential that these cells are safeguarded through the application of immunosuppressive techniques [35]. Conversely, the immunological dysregulation inherent in T1DM presents specific challenges, as the immune system may persist in targeting newly formed β-cells even after the creation. This holds particularly true in circumstances where immunosuppressive treatment fails to meet adequate levels. The successful outcome of these therapies hinges on achieving a balance between promoting β-cell regeneration and managing the immune response [36].

On the other hand, T2DM is marked by insulin resistance and β-cell dysfunction, which arise from chronic metabolic stress [37]. The findings of this study suggest that therapies utilising stem cells show a limited enhancement in C-peptide levels, implying that regenerated β-cells still face metabolic challenges in T2DM. The presence of insulin resistance in T2DM could potentially reduce the effectiveness of stem cell-based therapies, as noted by N. Yang *et al.* [38]. This holds particularly true when the underlying metabolic issues, such as hyperglycaemia, obesity, and chronic inflammation, are not simultaneously addressed. The therapeutic effects of regenerated β-cells may be constrained, as the operational efficiency could be compromised if the upstream variables remain unaddressed [39]. Moreover, the long-term safety profile of stem cell therapy remains to be determined, especially concerning the risks of cancer development or unintended differentiation of stem cells [40].

It is crucial to highlight that while stem cell therapies may hold promise for success, there are several potential risks involved, necessitating a careful approach. The variability in the outcomes of different regimens represents a significant concern. The effectiveness of these therapies is influenced by various factors, such as the quality of the stem cells, the delivery method employed, and the standard of care administered post-transplant. Furthermore, the source of stem cells – whether derived from autologous or allogeneic donors – may significantly affect both the efficacy and safety of the treatment, as allogeneic transplants carry an inherent risk of immune rejection, while autologous approaches may be limited by the quality of the patient's own cells. The variety of outcomes reported in the trials included in this meta-analysis highlighted the lack of standardisation in clinical protocols, which complicates the ability to compare results across different studies.

Conclusions

The pooled effect of fasting C-peptide levels showed a slight, non-significant improvement in T1DM patients, with an MD of 0.04 (95% CI: -0.09, 0.18; p = 0.51), suggesting no substantial impact on β-cell regeneration or preservation. In contrast, T2DM patients exhibited a modest, though still non-significant, improvement in C-peptide levels (MD = 0.09, 95% CI: -0.03, 0.21; p = 0.13), pointing to some potential for stem cell therapy in enhancing β-cell function in this population. This suggests that stem cell therapies may be more effective in T2DM patients, where metabolic stress is the primary factor affecting β-cell function. However, contrary to expectations, an increase in HbA1c levels was observed in both T1DM and T2DM patients, indicating a worsening of glucose control, particularly in T2DM, with a statistically significant mean difference of 0.71 (95% CI: 0.27, 1.15; p = 0.002). This suggests that while stem cell therapies may offer some benefits in preserving β-cell activity, such therapies do not result in better glycaemic control and may potentially exacerbate metabolic issues. These findings underscored the complexity of using stem cell therapies for diabetes management, especially in cases where insulin resistance or autoimmune destruction significantly impairs β-cell function.

The results of this meta-analysis were influenced by several biases, including missing data and confounding variables, which could distort the actual effectiveness of stem cell therapies. Moreover, the variability in study designs, stem cell types, and follow-up durations further complicates the interpretation of results. Therefore, stem cell-based regenerative therapies show modest promise for β-cell preservation in T2DM, but further research is required to evaluate the long-term efficacy, safety, and impact on overall diabetes management. Future studies should aim to standardise protocols, include larger sample sizes, and incorporate more comprehensive outcome measures, including quality of life and adverse events, to better inform clinical decision-making. Additionally, personalised approaches that account for the distinct pathophysiological mechanisms of T1DM and T2DM could enhance the therapeutic potential of stem cell therapies, offering more tailored and effective treatments for patients suffering from these chronic conditions. The need for rigorous, long-term clinical trials remains essential to better inform clinical decision-making and optimise the integration of regenerative therapies into mainstream diabetes management.

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Conflict of Interest

None.

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Порівняльна ефективність регенеративних методів лікування для збереження β-клітин при цукровому діабеті: метааналіз

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Анотація. Цукровий діабет, який пов'язаний з прогресуючою втратою β-клітин підшлункової залози, що призводить до дефіциту інсуліну та гіперглікемії, є глобальною проблемою охорони здоров'я. Регенеративні методи лікування, включаючи терапію стовбуровими клітинами мають потенціал для вирішення проблеми виснаження β-клітин та поліпшення результатів лікування діабету. Метою цього огляду було порівняння ефективності регенеративних методів лікування на основі стовбурових клітин для лікування пацієнтів з цукровим діабетом 1 та 2 типу. При проведенні цього огляду основними базами даних для звернення були PubMed, ClinicalTrials.gov та Google Scholar. Аналіз 9 досліджень, включаючи 5 рандомізованих контрольованих випробувань та 4 нерандомізованих дослідження, виявив помірне поліпшення рівнів С-пептиду, особливо у пацієнтів з цукровим діабетом 2 типу, із середньою різницею 0,09 (95 % довірчий інтервал: -0,03, 0,21; р-значення = 0,13), що свідчить про певну користь для збереження β-клітин. Однак терапія не показала поліпшення рівня глікованого гемоглобіну, спостерігалося підвищення рівня глікованого гемоглобіну із середньою різницею 0,71 (95 % довірчий інтервал: 0,27, 1,15; р-значення = 0,002), що вказує на погіршення контролю глюкози, особливо у пацієнтів з цукровим діабетом 2 типу. Хоча терапія стовбуровими клітинами є перспективною для збереження β-клітин, було виявлено, що вона не покращує глікемічний контроль. Це дослідження має важливе значення для клініцистів, які займаються лікуванням діабету, особливо тих, хто досліджує регенеративні методи лікування 1 та 2 типів цукрового діабету, і підкреслює необхідність індивідуалізованих терапевтичних стратегій, що враховують особливості патофізіологічних механізмів цих типів діабету

Ключові слова: терапія стовбуровими клітинами; регенеративна медицина; рівні С-пептиду; рівні HbA1C; контроль глікемії