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REVIEW
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Effectiveness of human induced pluripotent stem cell-derived β-like cell/islet transplantation in animal models of diabetes: A meta-analysis of preclinical studies

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Abstract: Emerging approaches in regenerative medicine for the treatment of diabetes have attracted attention. This meta-analysis aimed to evaluate the effectiveness of human induced pluripotent stem cell (hiPSC)-derived β-like cell/islet transplantation in animal models of diabetes. Studies using strictly controlled designs to assess hiPSC-derived β-like cell/islet transplantation were included. A reduction in blood glucose (BG) levels and improvement on the glucose tolerance test (GTT) served as indices to assess effectiveness. Twelve studies published between January 1, 2016 and December 31, 2025 were included. Pooled evidence indicates that transplantation of hiPSC-derived β-like cells/islets is associated with significant reductions in BG levels from four weeks to two months post-transplantation, with hypoglycemic effectiveness tending to increase over time. Improvements in glucose tolerance were also consistently observed. Overall, this meta-analysis synthesizes current preclinical evidence and identifies key areas where further research is needed to clarify translational and potential clinical applications.

***Keywords*:** diabetes, hiPSC derived β-like cells, islet, hypoglycemic effects, regenerative medicine

1. Introduction

Diabetes, and particularly type 2 diabetes (T2D), is a major public health concern that must be faced by governments worldwide as lifestyles change and populations age (*1*). Although hypoglycemic therapy or administration of exogenous insulin can effectively control blood glucose (BG) and improve the quality of life in patients, thus far there is still no specific treatment that can cure diabetes. The core problem lies in restoring islet function, which ensures that enough β cells generate sufficient endogenous insulin. Islet transplantation is a plausible treatment option. However, it cannot be widely used because of several well-known ethical and technological problems. Accordingly, emerging approaches in regenerative medicine are considered a beacon of hope for diabetes treatment.

The conventional approach involves the transplantation of pancreatic progenitor cells or islet organoids induced from human pluripotent stem cells (hPSCs). Technology for differentiating hPSCs into pancreatic progenitors and β-like cells is becoming increasingly mature. Our previous study provided a robust approach to induce vascularized pancreatic organoids from hPSCs by modulating WNT signaling with CHIR99021 in mTeSR1 and incorporating VEGFA (*2*). Although the effectiveness of transplantation of hPSC-derived β-like cells has been demonstrated in both animal and human studies (*3*), potential risks, such as technological difficulties (complicated differentiation processes, cancerization, and allograft rejection) and ethical risks (source of stem cells), cannot be ignored. Human induced pluripotent stem cells (hiPSCs) derived from somatic cells are a next-generation approach in regenerative medicine. Previous studies have focused on inducing β-like cells using somatic cells *in vitro* (*4,5*). Subsequent studies have evaluated the effectiveness of β-like cell transplantation in animal models (*6-10*). Recently, with the development of the concept of "organoids" researchers have attempted to "produce" islet organoids from hiPSCs *in vitro* and then transplant

them into animal models (*11,12*). A handful of reports on human patients are available (*3,13*). Although these reports documented the satisfactory effectiveness of transplanting islet-like organoids, they commonly suffer from small sample sizes, which precludes the obtaining of more convincing evidence. Due to the limitations of human studies, more useful information, such as the transplantation dose/site, approach, adverse events, and long-term effects, cannot be collected. Nevertheless, the massive demand for cellular therapy research on the bench and at the bedside mean that these issues are at the forefront during clinical use and experiments. Thus, animal studies are being considered because the available literature is far more extensive than that for human studies, offering more in-depth exploration. In addition, our previous studies focused on regenerative medicine using hPSCs (*2,14*) and hiPSCs (*15-17*) to generate a variety of functional cells and organoids, such as pancreatic progenitors and β-like cells (*2*), functional hepatobiliary organoids (*14,15,17*), and cardiomyocytes (*16*). Based on our experience using hPSCs and hiPSCs, along with our insights in this field, we believe that a meta-analysis that comprehensively investigates the effectiveness of hiPSC-based transplantation in diabetes is needed and timely.

Accordingly, we designed the current meta-analysis in compliance with the PRISMA guidelines (*18*) to investigate the effectiveness of transplantation of hiPSC-derived β-like cells/islets in treating diabetes. Due to the limited number of human studies, the current study focused on available animal studies.

2. Literature search strategies and analytical approach

2.1. Literature search strategy

A comprehensive electronic search was conducted using eight medical search engines (the PubMed, Cochrane Library, ISI Web of Science, Embase, CNKI, SinoMed, Wanfang, and Weipu databases). This study was not registered in any public database. Articles in English from January 1, 2016 to December 31, 2025 were included in the review. The following terms were used for the search: ("Induced Pluripotent Stem Cells"[MeSH] OR "hiPSC"[Title/Abstract] OR "iPS cells"[Title/Abstract] OR "induced pluripotent stem cell*"[Title/Abstract]) AND ("Islets of Langerhans"[Mesh] OR "pancreatic islet*"[Title/Abstract] OR "islet cell*"[Title/Abstract] OR "beta cell*"[Title/Abstract] OR "β cell*"[Title/Abstract] OR "insulin-producing cell*"[Title/Abstract]) AND ("Diabetes Mellitus"[MeSH] OR "diabetes *"[Title/Abstract]). The references of important studies were also manually reviewed to identify more potentially relevant studies. Inclusion and exclusion criteria were established based on the PICOS criteria, all the included studies used data of animal experiments (Table 1).

2.2. Data extraction and evaluation of study quality

First, two authors (RC and JX) searched the databases and performed primary screening by reading the titles and abstracts of the articles obtained. Subsequently, a third author (XS) read the full texts and recommended potentially eligible studies. Finally, these studies were cross-checked by senior authors (TA and FW), and the final eligible studies were determined. Two independent authors (JK and GW) extracted data from the eligible studies for further investigation. Information including authors, title, publication time, experimental design (subjects, sample size, setting of treatment/control groups, randomization, blinding, intervention, and outcome measures), and results was acquired. In line with the aim of this study, changes in BG levels and improvement on the glucose tolerance test (GTT) served as indices to assess the effectiveness of transplantation. The software Getdata Graph Digitizer (V2.26.0, *http://getdata-graph-digitizer.com*) was used to assist in data acquisition. In this study, the time points for BG monitoring (weeks 1, 2, 3, and 4) and oral glucose tolerance test (OGTT; 30, 60, 90, and 120 min) were standardized as evaluation nodes. Since the raw data were primarily extracted from the original figures using digitalization software, this standardization was performed to minimize data heterogeneity and ensure comparability across studies, thereby meeting the statistical requirements for meta-analysis. Discussions were conducted weekly to reach a consensus. Finally, a third-party author (NL) checked all data before they were submitted for meta-analysis.

Study quality was assessed using the SYRCLE Risk of Bias Tool (*19*). This tool included 10 entries, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Egger's test (*20*)

Table 1. PICOS criteria for inclusion and exclusion of studies in the current study

Parameters	Inclusion criteria	Exclusion criteria
Population	Animal models of diabetes	Non-animal models of diabetes
Intervention	Treatment using hiPSC-derived β cells	Treatment not using hiPSC-derived β cells
Comparison	hiPSC-derived β cells *vs.* Blank control or Sham group	Without using parallel control
Outcome	BG levels, GTT outcomes	BG levels and GTT outcomes were not reported

Abbreviations: BG, blood glucose; GTT, glucose tolerance test; hiPSC, human induced pluripotent stem cells.

was used to analyze publication bias. The potential for publication bias regarding BG levels and GTT outcomes was initially assessed *via* visual inspection of funnel plots. Publication bias was further evaluated using Egger's linear regression test. W4 for BG levels and 90 min on the GTT were selected for Egger's test because these two time points were included in the largest number of studies. Two authors (RC and TA) conducted the assessments of all included articles.

2.3. Statistical analysis

This study was designed and performed in accordance with the Cochrane Handbook (*21*) and PRISMA guidelines (*22*). The software Stata SE 16 (StataCorp LLC, TX, USA) was used for meta-analysis. Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for continuous data. WMDs were selected rather than standard mean differences (SMDs) for the following reasons: *i*) all indices (BG levels and GTT outcomes) were expressed in mg/dL; *ii*) the magnitude of improvement in all indices was the most important parameter in this study, and WMD can provide quantitative data; *iii*) the heterogeneity of included studies was not caused by the method of measurement (such as measuring BG levels); and *iv*) we performed subgroup and sensitivity analyses to explore the causes of heterogeneity. The I^2 index was used to evaluate heterogeneity among the studies. If the *p*-value was ≥ 0.1 and I^2 was ≤ 50%, the study was considered homogeneous, and a fixed-effects model was used. If $p < 0.1$ and $I^2 > 50\%$, the study was considered heterogeneous, and a random-effects model was used. Statistical significance was set at $p < 0.05$. The software RevMan (V5.4; Cochrane, London, UK) was also used to evaluate the quality of the studies.

2.4. Subgroup analysis and sensitivity analysis

Subgroup analyses were performed to identify potential sources of inconsistency and to evaluate the robustness of the pooled estimates. The predefined grouping criteria for BG levels included cell source (β cells *vs.* organoid-derived β-like cells), cell infusion dose (low dose < 5.0×10^6 *vs.* high-dose ≥ 5.0×10^6), and mouse strain (NOD-SCID *vs.* SCID-Beige). The predefined grouping criteria for the GTT included an OGTT *vs.* an intraperitoneal GTT (IPGTT). To assess the stability of the pooled estimates of BG levels, a leave-one-out sensitivity analysis was performed for each time point. BG levels and GTT parameters at each time point were statistically analyzed. These analyses aimed to determine whether experimental variations significantly influenced therapeutic outcomes and contributed to overall statistical diversity.

3. Key research findings

3.1. Characteristics of the included studies

As shown in Figure 1, 12 studies published after 2016 were included in this study. Table 2 shows the characteristics of the included studies. All 12 studies (published between 2016 and 2025) were in English and involved transplantation of iPSC-derived β-cells (studies were published between 2016 and 2022) (*6-10,18,23*) or iPSC-derived islet organoids (studies were published between 2022 and 2025) (*3,11-13,24*). All studies used data of animal studies and no human studies were included in the review, despite two studies (*3,13*) included human data. Streptozotocin-induced diabetic mice were used in these studies. Of the 12 studies, seven used NOD-SCID mice (*6-10,12,24*), whereas five used SCID-Beige mice (*3,11,13,18,23*). Most studies implanted cells/islet organoids surrounding the kidney capsule (*3,6-8,10-13,18,23*), whereas one study used intraperitoneal and subcutaneous transplantation (*9*), and one study transplanted islet organoids at the dorsal subcutaneous site (*24*). The main outcome measures included BG levels and improvement on the GTT (intraperitoneal or oral). The detailed characteristics of the included studies are listed in Table 2.

3.2. Quality assessment of included studies

The quality of the included studies was assessed using the

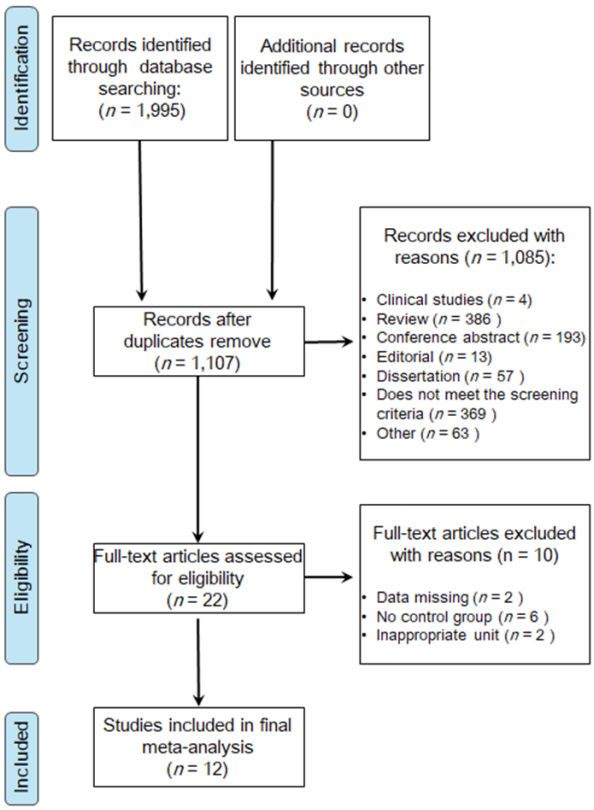

Figure 1. Flow chart for the search strategy and selection of studies.

Table 2. Characteristics of the included studies

Study (*Ref.*)	Sample size	Animal	Number of hiPSC-derived cells	Transplantation site	Endpoints
hiPSC-derived β-like cells					
Yoshihara 2016 (*6*)	13	NOD-SCID mice	1.0×10^7	Kidney capsule	BG levels, Human C-peptide levels
Kondo 2017 (*7*)	3/3	NOD-SCID mice	2.0×10^6	Renal subcapsules	BG levels
Yabe 2017 (*8*)	20	NOD-SCID mice	4.0×10^6	Kidney capsules	BG levels, OGTT outcomes, Human C-Peptide
Fukuda 2019 (*9*)	4/4	NOD-SCID mice	1.2×10^7	Intraperitoneal and subcutaneous administration	OGTT outcomes
Yabe 2019 (*10*)	7	NOD-SCID mice	6.0×10^6	Left kidney capsule	BG levels, OGTT outcomes, Human C-peptide levels
Yang 2020 (*23*)	8/8	SCID-Beige mice	1.0×10^7	Left renal capsule	BG levels, OGTT outcomes
Du 2022 (*18*)	17	SCID-Beige mice	3.0×10^6	Kidney capsules	IPGTT outcomes, Human C-peptide levels
hiPSC-derived islets					
Takaichi 2022 (*24*)	4/4	NOD-SCID mice	7.68×10^5	Dorsal subcutaneous site	BG levels, IPGTT outcomes
Wang 2024 (*13*)	20	SCID-Beige mice	3.0×10^6	Kidney capsule	IPGTT outcomes
Wu 2024 (*3*)	5	SCID-Beige mice	0.6 or 3×10^4	Kidney capsule	BG levels
Chen 2025 (*12*)	8/5/9	NOD-SCID mice	5.0×10^6	Renal peritoneum	BG levels, IPGTT outcomes, Body
Dadheech 2025 (*11*)	15	SCID-Beige mice	1.5×10^6	Renal sub capsule	BG levels, IPGTT outcomes, Human C-peptide levels

Abbreviations: BG, blood glucose; GTT, glucose tolerance test; IPGTT, intraperitoneal glucose tolerance test; hiPSC, human induced pluripotent stem cells; OGTT, oral glucose tolerance test.

SYRCLE Risk of Bias Tool. Figure 2 was prepared based on the results of the SYRCLE-based quality assessments. Detailed information on each article is provided in the Supplementary Material. As shown in Figure 2, two studies adopted a randomization design (*23,24*), whereas two studies did not perform randomization (*7,11*). The randomization status of the other eight studies was also unclear. Information regarding concealment and blinding of the researchers was unclear (Figure 2A). Since these studies involved only animals and all indices were objective, blinding of the animals was acceptable (*25*). Attrition and reporting biases were judged to be low risk because the experimental protocols were available in all of the studies. In addition, all of the studies reported homogeneity of the baseline data between the treatment and control groups (Figure 2B). Other biases defined by the SYRCLE Risk of Bias Tool were identified as low risk.

Figure 3 shows the results of Egger's test. The funnel plot for BG levels (Figure 3A) revealed that most study coordinates were clustered to the left of the mean effect size (negative WMD region), suggesting a general consensus on the effectiveness of the intervention at lowering glucose. However, pronounced asymmetry was observed; data points in the right-hand region (WMD ≥ 0) were sparse, and particularly among small-sample studies with larger standard errors. This void suggests a potential risk of publication bias, in which studies yielding negative or non-significant results may remain unpublished. Egger's linear regression test yielded a regression intercept (bias) of 1.248 with a *p*-value of 0.637 ($p > 0.05$) (Figure 3B), indicating no statistically significant small study effects. These results suggest that any observed asymmetry in the funnel plot was due to genuine inter-study heterogeneity or other factors rather than systematic publication bias. The funnel plot for GTT outcomes (Figure 3C) exhibited a markedly asymmetrical distribution. Most of the studies were concentrated in the negative effect size region, with a conspicuous absence of corresponding studies in the right-hand (positive effect size) quadrant. This pattern further indicates the potential omission of small-sample studies with negative outcomes. Egger's linear regression test yielded a bias of 1.48, with a *p*-value of 0.169 ($p > 0.05$) (Figure 3D). Since the *p*-values for both primary outcomes exceeded the 0.05 threshold, one can conclude that there was no evidence of significant publication bias in this meta-analysis.

3.3. Outcome measures

3.3.1. BG levels

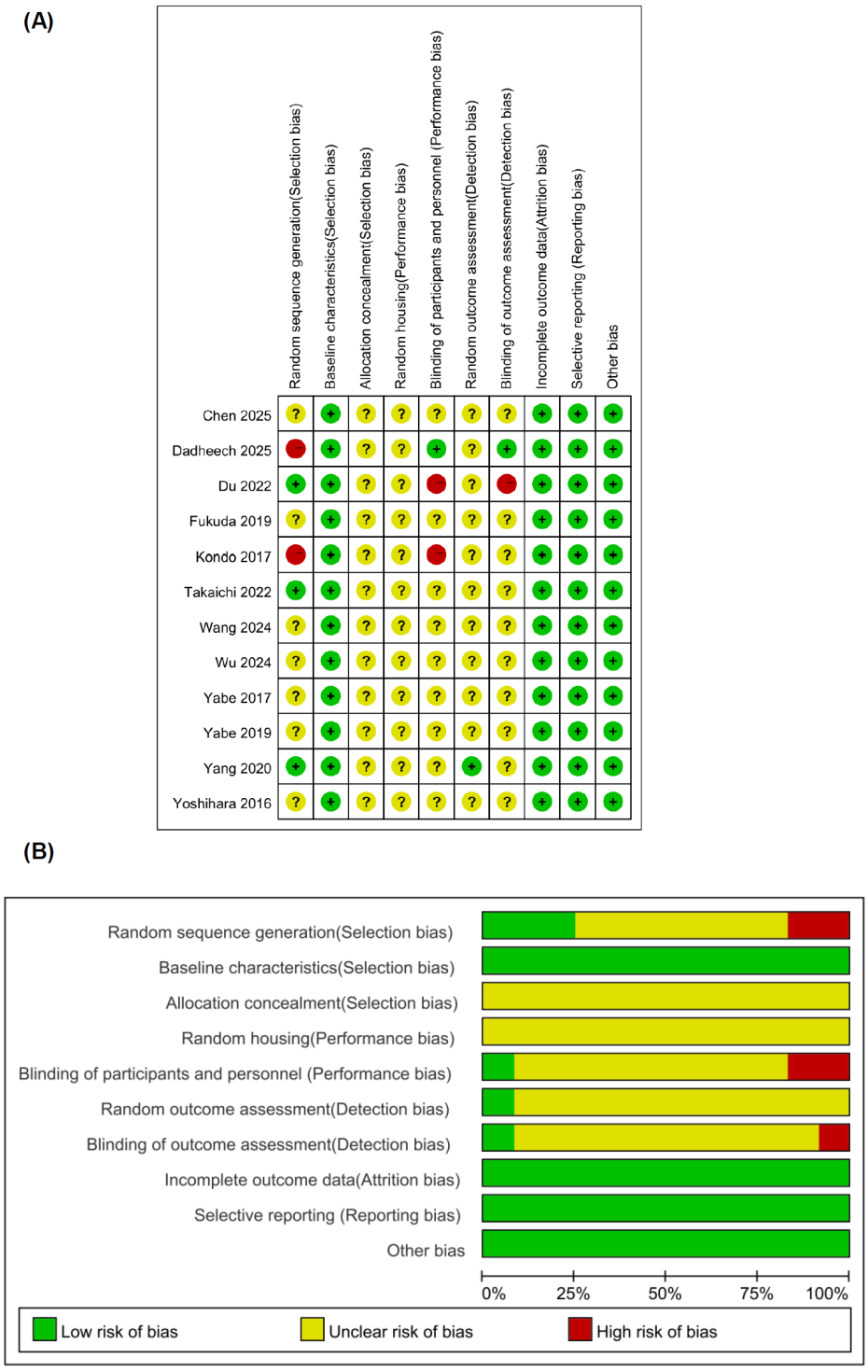

Figure 2. Potential risk of bias in the current study. (A) Risk of bias in the included studies; **(B)** Summary of the risk of bias in the included studies.

Figure 4 shows the decrease in BG levels after transplantation of hiPSC-derived β-cells or islets (treatment *vs.* control). All results indicated that transplantation of hiPSC-derived β-cells or islets led to a decrease in BG levels from one week (W1) to two months after treatment. After transplantation in W1, BG levels began to decrease. Such changes in BG levels were significant (n = 97, WMD = -134.39, 95% CI [-182.10 – -86.68], $p < 0.001$). The homogeneity test (X^2 = 289.05, p = 0.00, I^2 = 97.22%) indicated a high level of heterogeneity among the studies (Figure 4A). After transplantation in W2, BG levels also significantly decreased (n = 97, WMD = -131.45, 95% CI [-194.34 – -68.54], $p < 0.001$). The homogeneity test (X^2 = 442.03, p = 0.00, I^2 = 97.78%) indicated a high level of heterogeneity among these studies (Figure 4B). After

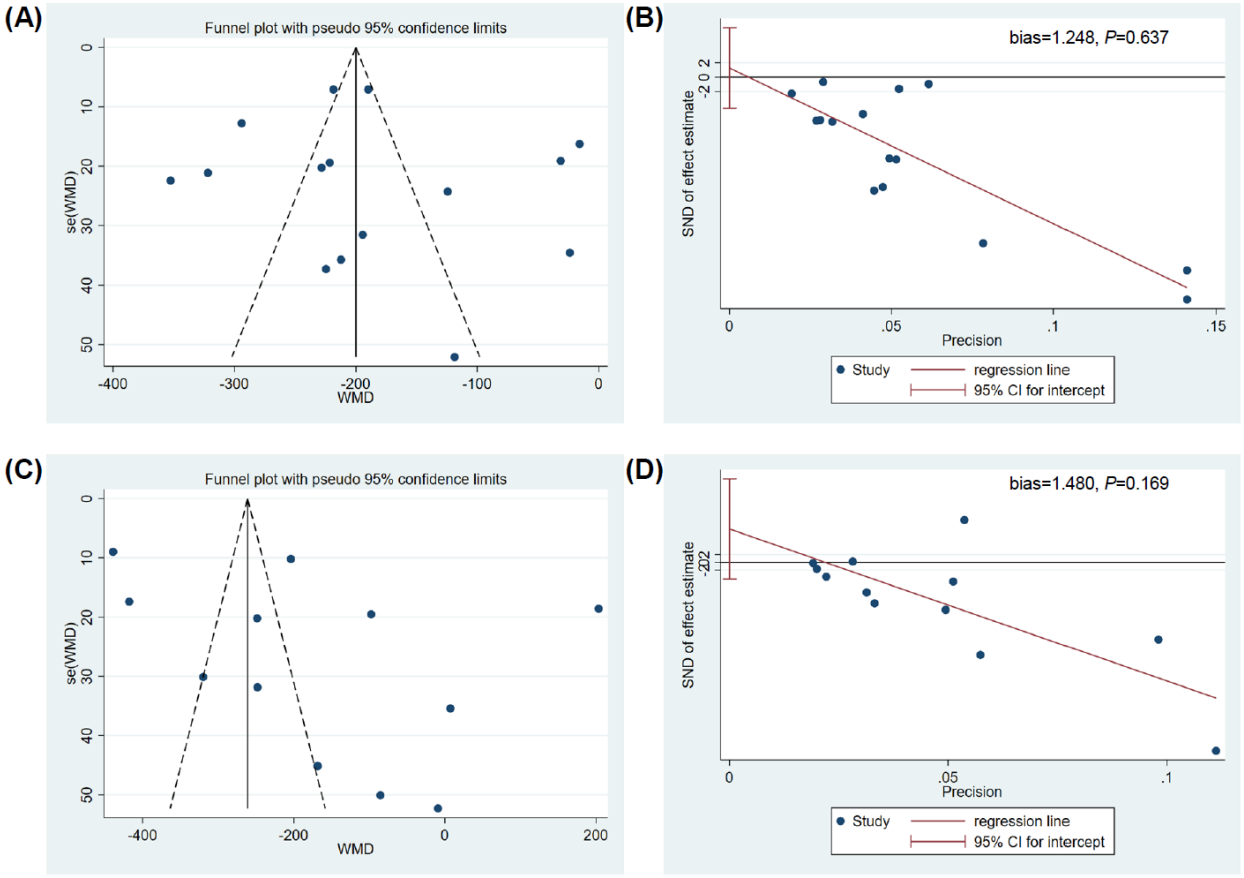

Figure 3. Results of Egger's test. (A) Funnel plot of the standard error by WMD for blood glucose BG levels; **(B)** Egger's linear regression test for publication bias in BG levels; **(C)** Funnel plot of the standard error by WMD for GTT outcomes; **(D)** Egger's linear regression test for publication bias for GTT outcomes.

transplantation in W3, BG levels also significantly decreased (n = 96, WMD = -170.46, 95% CI [-223.96 – -116.95], p < 0.001). The homogeneity test (X^2 = 444.20, p = 0.00, I^2 = 97.70%) indicated a high level of heterogeneity among these studies (Figure 4C). After transplantation in W4, BG levels decreased significantly (n = 95, WMD = -185.97, 95%CI [-228.58 – -133.36], p < 0.001). The homogeneity test (X^2 = 391.23, p = 0.00, I^2 = 97.51%) indicated a high level of heterogeneity among these studies (Figure 4D). Four studies (*6,10-12*) conducted long-term (two months after treatment) observations, and BG levels significantly decreased further (n = 40, WMD = -317.23, 95% CI [-362.41 – -272.05], p < 0.001). The homogeneity test (X^2 = 5.40, p = 0.15, I^2 = 66.59%) indicated a relatively low level of heterogeneity among the studies (Figure 4E). The data imply that the effect of lowering BG levels tends to become stronger and that the heterogeneity among studies tends to decrease over time after transplantation.

3.3.2. Results on the GTT

Figure 5 shows the reduction in BG levels after the GTT (treatment *vs.* control). Thirty min after glucose administration, BG levels decreased significantly (n = 93, WMD = -192.89, 95% CI [-273.28 – -112.50], p < 0.001). The homogeneity test (X^2 = 1526.58, p = 0.00, I^2 = 98.64%) indicated a high level of heterogeneity among these studies (Figure 5A). Sixty min after glucose administration, BG levels decreased significantly (n = 93, WMD = -238.71, 95% CI [-324.68 – -152.74], p < 0.001). The homogeneity test (X^2 = 1161.37, p = 0.00, I^2 = 98.55%) indicated a high level of heterogeneity among these studies (Figure 5B). Ninety min after glucose administration, BG levels decreased significantly (n = 88, WMD = -206.52, 95% CI [-287.86 – -125.18], p < 0.001). The homogeneity test (X^2 = 643.47, p = 0.00, I^2 = 98.12%) indicated a high level of heterogeneity among these studies (Figure 5C). One hundred and twenty min after glucose administration, BG levels decreased significantly (n = 75, WMD = -229.35, 95% CI [-325.10 – -133.59], p < 0.001). The homogeneity test (X^2 = 409.73, p = 0.00, I^2 = 97.99%) indicated a high level of heterogeneity among these studies (Figure 5D). Accordingly, improvement on the GTT was evaluated in this study.

3.4. Subgroup analysis and sensitivity analysis

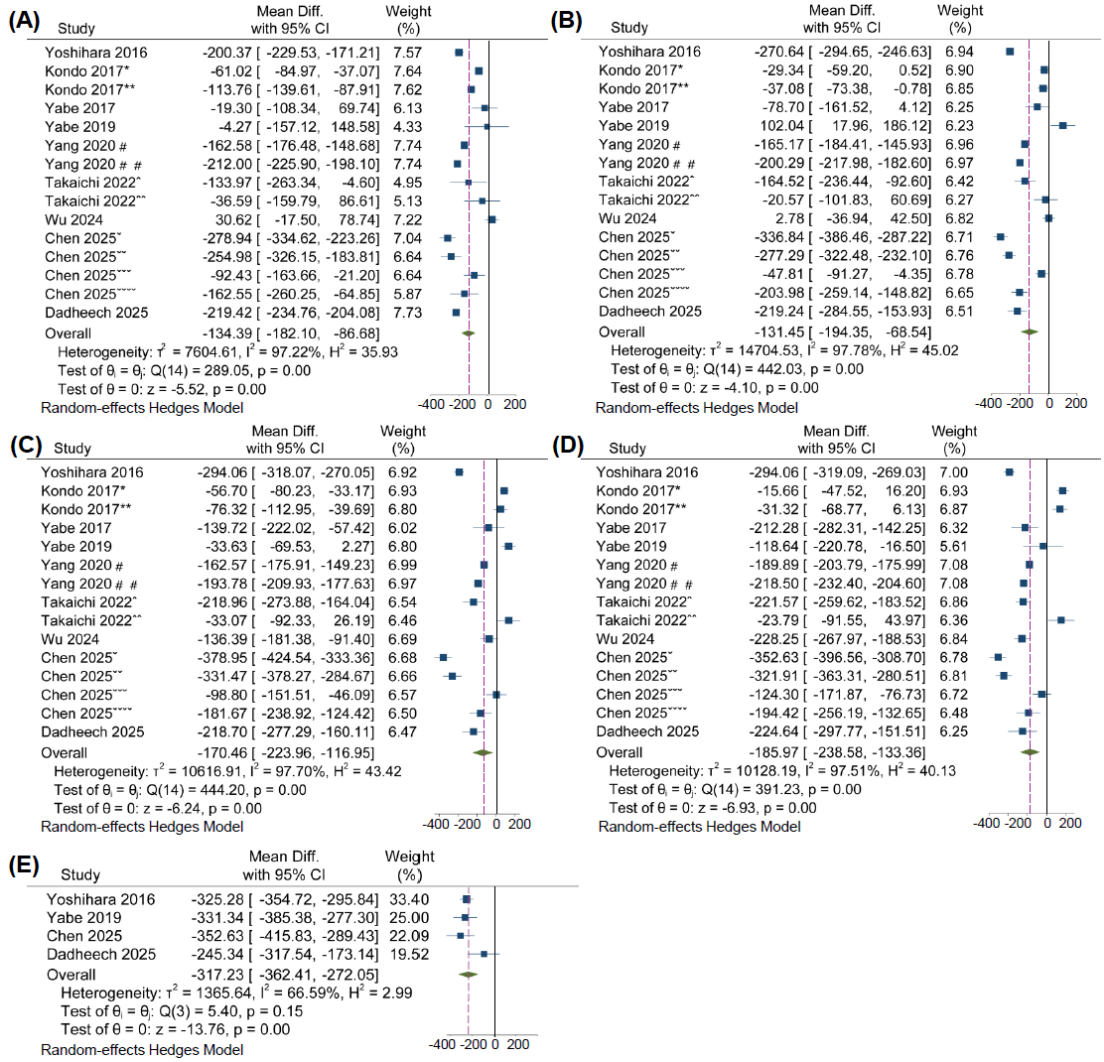

Figure 4. The effectiveness of hiPSC-derived-β cell/islet transplantation at reducing BG. (A) Forest plot of reduction in BG 1 week (W1) after transplantation; **(B)** Forest plot of reduction in BG W2 after transplantation; **(C)** Forest plot of reduction in BG W3 after transplantation; **(D)** Forest plot of reduction in BG W4 after transplantation; **(E)** Forest plot of reduction in BG 2 months after transplantation. *Abbreviations*: BG, blood tolerance. List of symbols in the figures (The different symbols represent the attributes of the intervention): *INS+-hiPSCs-4Fs, **INS+-hiPSCs-4Fs + SCG, #IPCs-scrambled-shRNA, ##IPC-shRNA-LSD1-927, ^vascularized hiPS β-cell spheroid tissue, ^^non-vascularized hiPS β-cell spheroid tissue, ˇβ cell-hiPSCs, ˇˇMVF-vascularized islets, ˇˇˇHUVEC-vascularized islets, ˇˇˇˇun-vascularized islets.

3.4.1. Subgroup analysis of BG levels

Table 3 shows the results of the subgroup analysis (primary β cells *vs.* organoid-derived β-like cells). The heterogeneity test revealed that the I^2 values for all indices remained substantially high and did not decrease significantly within the subgroups (Table 3). These findings suggest that the observed inter-study heterogeneity was not primarily attributable to the β-cell source, indicating that the origin of the cells did not significantly moderate the pooled treatment effects in this study.

When a low dose was compared to a high dose, the heterogeneity of BG levels tended to decrease in week 2 (I^2 = 86.7%, $p < 0.001$). To further isolate the sources of inconsistency, a sensitivity analysis was performed while excluding one study (Dadheech 2025) that utilized a different mouse strain. Once it was excluded, the heterogeneity of the outcome significantly decreased further to I^2 = 68.8% (p = 0.012). These findings suggest that the substantial heterogeneity observed in the primary analysis is likely attributable to variations in cell dosage and animal strains.

Results for the mouse strain indicated a marked decrease in the heterogeneity of BG levels within the SCID-beige subgroup in both week 3 (I^2 = 77.8%, p = 0.004) and week 4 (I^2 = 69.1%, p = 0.021) compared to the overall pooled analysis. These findings indicate that the inherent biological variations between different immunodeficient mouse strains are likely the primary driver of the high level of heterogeneity observed in this study.

3.4.2. Subgroup analysis of GTT outcomes

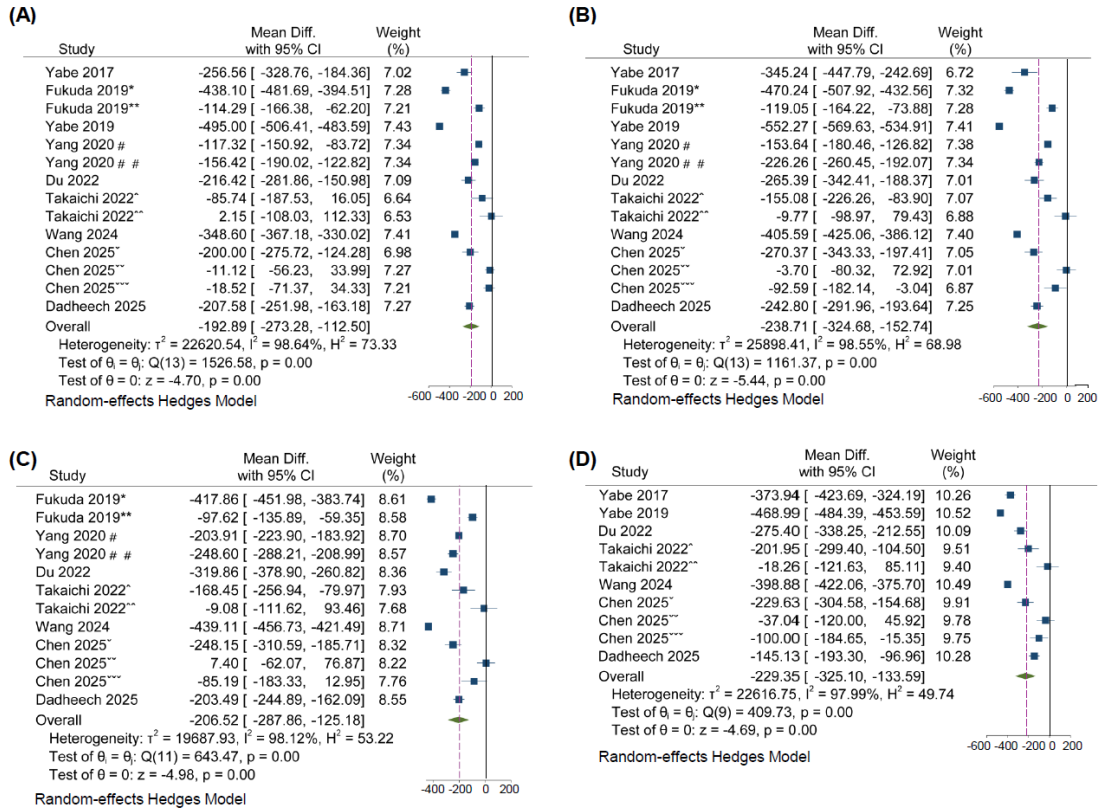

Figure 5. Effectiveness of hiPSC-derived-β cell/islet transplantation at improving GTT outcomes. (A) Forest plot of improvement on the GTT 30 min after glucose injection; **(B)** Forest plot of improvement on the GTT 60 min after glucose injection; **(C)** Forest plot of improvement on the GTT 90 min after glucose injection; **(D)** Forest plot of improvement on the GTT 120 min after glucose injection. *Abbreviations*: GTT, glucose tolerance test. List of symbols in the figures (The different symbols represent the attributes of the intervention): *fiber i.p., **fiber s.c., #IPCs-scrambled-shRNA, ##IPC-shRNA-LSD1-927, ˆvascularized hiPS β-cell spheroid tissue, ˆˆnon-vascularized hiPS β-cell spheroid tissue, ˇMVF-vascularized islets, ˇˇHUVEC-vascularized islets, ˇˇˇun-vascularized islets.

Table 3. Subgroup analysis to explore the sources of heterogeneity in blood glucose and glucose tolerance outcomes

Assessed outcomes	β-cell source	Heterogeneity (I^2, p)
BG level (1 W)	β cells	$I^2 = 95.8\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 94.7\%$, $p < 0.001$
BG level (2 W)	β cells	$I^2 = 97.7\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 94.9\%$, $p < 0.001$
BG level (3 W)	β cells	$I^2 = 98.1\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 92.5\%$, $p < 0.001$
BG level (4 W)	β cells	$I^2 = 97.8\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 91.6\%$, $p < 0.001$
BG level (2 M)	β cells	$I^2 = 0.0\%$, $p = 0.744 > 0.05$ (No significant heterogeneity)
	organoid-derived β-like cells	N/A
GTT outcome (30 min)	β cells	$I^2 = 99.3\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 96.2\%$, $p < 0.001$
GTT outcome (60 min)	β cells	$I^2 = 99.3\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 97.5\%$, $p < 0.001$
GTT outcome (90 min)	β cells	$I^2 = 97.7\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 99.5\%$, $p < 0.001$
GTT outcome (120 min)	β cells	$I^2 = 95.5\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 97.1\%$, $p < 0.001$

In the IPGTT subgroup using NOD-SCID mice, heterogeneity across all time points (30, 60, 90, and 120 min) was mitigated to varying degrees (I^2 = 80.5%, 87.6%, 88.6%, and 78.5%, respectively). And in the IPGTT subgroup combined with low-dose cell infusion, heterogeneity effectively decreased at the 90-min mark (I^2 = 68.0%, p = 0.044). These findings indicate that discrepancies in the form of GTT administered are a significant driver of the high level of heterogeneity observed in this meta-analysis.

3.4.3. Sensitivity analysis of BG levels

In week 1, the pooled WMD remained remarkably stable, with 95% CIs fluctuating narrowly between -1.98 and -1.49, suggesting that no single study had excessive influence. In week 2, however, slight variations were observed; the lower and upper bounds of the CIs ranged from -2.30 to -1.10 and -1.80 to 0.80, respectively. Notably, the exclusion of the study by Wu *et al*. (*3*) or that by Chen *et al.* (*12*) caused the upper bound to approach or slightly transcend the line of no effect (WMD = 0), indicating that these specific trials were pivotal to the significance of the week 2 findings.

The results for weeks 3 and 4 exhibited a high level of integrity, with CIs ranging from -4.20 to -2.95 and -3.98 to -2.25, respectively. In both instances, the pooled estimates were not significantly attenuated by the removal of any individual study, and the CIs did not cross the null line. At the 2-month follow-up, exclusion of the study by Yoshihara *et al*. (*6*) shifted the CI to [-10.19, -7.47] compared to a range of [-7.47, -6.01] for other exclusions. This identifies the study by Yoshihara (*6*) as a high-contribution study; however, the overall direction and significance of the effects remain unchanged.

3.4.4. Sensitivity analysis of GTT outcomes

At 30 min, excluding individual studies yielded pooled effect sizes ranging from -3.11 to -0.10 (overall WMD: -2.48). Similarly, at 60 and 90 min, the recalculated effect sizes fluctuated between -2.98 and -0.54 (-2.30 overall) and -3.00 and -0.40 (-1.80 overall), respectively. At 120 min, marked stability was evident; the pooled results remained constant at -2.76 (95% CI: -3.05 to -2.47), despite the overall pooled estimate of -1.00.

4. Implications for practice and research

The current study performed a meta-analysis of 12 eligible studies to verify the effectiveness of hiPSC-based transplantation in the treatment of diabetes. Results revealed that the transplantation of hiPSC-generated-β cells (*6-10,18,23*) or stem cell-generated islets (*3,11-13,24*) led to a significant reduction in BG levels and improved GTT performance in animal models of diabetes. Importantly, the effectiveness of both cell and organoid transplantation increased over the transplantation period. This suggests the reliability of hiPSC-generated β-cells and islets within the follow-up period. To the extent known, this is the first meta-analysis to elucidate the effectiveness of hiPSC-based transplantation in treating animals with diabetes. The current findings may provide a working foundation for further use of this technology in clinical settings.

4.1. Study quality

This study used the SYRCLE Risk of Bias Tool to evaluate study quality (Figure 2 and Supplementary Materials, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=119*) and Egger's test to assess potential publication bias (Figure 3). A small number of studies were included, many of which did not report allocation concealment. However, all of the indices are objective, so this issue may not have influenced the final results (*25*). Egger's test was used to conduct a comprehensive evaluation of publication bias. Although the funnel plots exhibited a degree of visual asymmetry, Egger's linear regression test yielded no significant evidence of bias ($p > 0.05$) in both BG levels and GTT outcomes. This discrepancy suggests that the observed asymmetry likely stems from inherent inter-study heterogeneity rather than systematic suppression of negative findings. Consequently, the pooled estimates for BG levels and GTT outcomes in this meta-analysis are considered statistically stable and representative of the available evidence.

4.2. Reduction in BG levels

The most important issue in diabetes therapy is to control BG to a certain level and to avoid a large daily amplitude of glycemic excursions, regardless of the use of exogenous insulin, hypoglycemic medication, or any other therapy. In this regard, a reduction in BG levels is regarded as the most intuitive and one of the most important indices for evaluating the effectiveness of a certain treatment in patients and animal models. Accordingly, studies assessing the effectiveness of certain treatments have commonly adopted this index. In the field of regenerative medicine involving the transplantation of β-like cells or hiPSC-derived islets, a sustained reduction in BG levels often means successful generation of insulin-producing β-like cells/islets, or what are known as functional β-like cells/islets. Based on β-like cells/islets, an islet organoid should have a vascular structure to maintain a stable blood supply, enabling it to mimic a natural islet and to secrete insulin. The concept of islet organoids is still in its infancy. However, the basic index to evaluate the success of islet organoid generation remains a reduction in BG levels.

The follow-up period in most of the included studies was four weeks, and only four studies (*6,10-12*) conducted a relatively longer two-month follow-up. The meta-analysis suggested that transplantation of hiPSC-derived β-cells or islets reduced BG levels, and the hypoglycemic efficiency tended to increase from W1 to 2 months after treatment (Figure 4). However, the highly heterogeneous nature of the included studies resulted in different findings for each time point. The current results revealed that after transplantation in W1, BG levels began to decrease, except in one study (*3*) that transplanted hiPSC-derived islets (Figure 4A). Only one study (*10*) involving hiPSC-derived β-cells noted an increase in W2

(Figure 4B). Two studies (*7,10*) that transplanted hiPSC-derived β-cells and one study (*24*) that transplanted hiPSC-derived islets noted an increase in W3 (Figure 4C). One study (*7*) that transplanted hiPSC-derived β-cells and another (*24*) that transplanted hiPSC-derived islets noted an increase in W4 (Figure 4B). In the studies that ended two months after transplantation, no increase was noted, including two studies (*6,10*) that transplanted hiPSC-derived β-cells and two recent studies (*11,12*) that transplanted islet organoids. These findings confirmed that the hypoglycemic efficiency tended to increase over time. Studies noting an increase were found to have been conducted in earlier years, for example, that by Kondo *et al*. (*7*) and Yabe *et al*. (*10*) with hiPSC-derived β-cells and that by Takaichi *et al*. (*24*) with hiPSC-derived islets. One plausible interpretation of this is that it reflects the limitations of the technology at that time. Moreover, these findings imply that four weeks is too short a time to evaluate the amelioration resulting from transplantation since the BG levels were still unstable at that time point. However, the optimal time for evaluation needs to be studied further.

4.3. Amelioration of GTT outcomes

The GTT is commonly used to examine insulin sensitivity and islet function in patients with diabetes. In animal studies in regenerative medicine, the GTT is used to test the quality and quantity of insulin produced by β-like cells/islets. Results indicated that BG levels decreased significantly from 30 min to 120 min after glucose administration (Figure 5), confirming the quality and quantity of insulin secreted by the transplanted cells/islets.

4.4. Subgroup analysis and sensitivity analysis

4.4.1. Subgroup analysis

The multi-dimensional subgroup analyses performed in this study revealed that the source of β cells was not a primary contributor to the heterogeneity observed. Conversely, subgroups stratified by cell infusion dose, mouse strain, and the form of GTT administered exhibited a marked decrease in I^2 values. Although the heterogeneity in these subgroups did not consistently fall below the 50% threshold, its tendency to decline significantly identified these three factors as core drivers of statistical inconsistencies across studies. To enhance the robustness and reproducibility of future findings, an imperative step is to implement standardized experimental protocols, particularly by unifying cell dosages, selecting consistent animal models, and harmonizing the method of GTT administration. Moreover, expanding the sample size within a rigorous, standardized framework is essential to minimizing heterogeneity and ensuring the consistency of therapeutic evaluations in β-cell transplantation research.

4.4.2. Sensitivity analysis

Week 2 data from several studies might have influenced the results, but the overarching results from the sensitivity analysis of BG levels across all temporal intervals remained consistent. The consistency of the WMD and the fact that the 95% CIs remained entirely within the significant range confirm that the glycemic outcomes of this meta-analysis were statistically robust and highly reliable.

In the sensitivity analysis of GTT outcomes, data from all temporal intervals confirmed that the removal of any constituent study did not result in a substantial shift in the pooled WMD. The re-estimated effect sizes were consistent with the primary results, and all 95% CIs remained entirely on one side of the line of no effect (WMD = 0). Collectively, these results suggest that GTT outcomes in this meta-analysis are not influenced by any single study, thereby ensuring the overall reliability of the findings.

4.5. Strengths and weaknesses of the evidence

The current study assessed BG levels and improvement on the GTT, which are commonly and easily measured in animal studies, as indices. Studies on β-like cells and islet organoids were included, which helped to provide a general impression of the effectiveness of stem cell-based therapies to treat diabetes in animal models. The SYRCLE Risk of Bias Tool and Egger's test were used to confirm the quality of the included studies. Subgroup analyses and sensitivity analysis were performed to explore the causes of high heterogeneity. These analyses help to improve the interpretability and reliability of the results. Analysis of the data revealed the high level of effectiveness of the transplanted cells and islets. Moreover, results revealed improvement after transplantation, which implied the stability of the generated β-like cells/islets over time. These findings are promising for the future adoption of regenerative medicine approaches to cure patients with diabetes. The BG data imply that four weeks might be too short a time to evaluate the efficiency of implanted cells/islets, which future studies may wish to account for.

However, the current study had several limitations. First, the limited number of eligible studies with a high level of heterogeneity might have led to biased conclusions. Second, inter-reviewer agreement based on Cohen's kappa was not tested during data extraction, and this may have diminished the reliability of this study. Third, other important diabetes-related indices, such as C-peptide levels (*13*), HbA1c levels, and BETA-2 scores (*26*), are indispensable to a comprehensive understanding of the effects of transplantation on diabetes, but they were not tested here. A small number of studies have

used those indices, but their methodologies were varied and heterogeneous. Most of the identified studies did not use those indices, precluding their inclusion in this study. A lack of these key indicators may weaken the strength of the conclusions. Accordingly, the authors propose adopting a standardized methodology for these important diabetes-related indices so that they can be compared among different studies. Fourth, the long-term effectiveness of the treatment could not be evaluated. Fifth, vascularization could not be evaluated. Vascularization is an important topic in β-cell replacement therapy, and whether islet organoids are vascularized or non-vascularized may play a crucial role in their long-term survival. However, only a few of the included studies (*12,24*) compared the effects of vascularized and non-vascularized islets. Sixth, due to the high heterogeneity of this study, other than subgroup and sensitivity analysis, more rigorous analysis, such as meta-regression might be helpful to get robust evidence. Seventh, we used Egger's test to evaluate the potential publication bias, however, due to the insufficient nature of the available literature (12 literatures) to date, this might cause biased results. Future studies should address the issues mentioned here for a more in-depth and comprehensive analysis.

In summary, transplantation of hiPSC-derived β-like cells/islets to treat diabetes is indeed a promising approach for both patients and clinicians, but it is still far from clinical use because many technological challenges must be addressed. The first consideration is safety. An example is the possibility of tumorigenicity or overgrowth of the transplanted cells/organoids. Any adverse events, such as transplantation-induced systemic immune responses and reactions at the transplantation site, should be evaluated. The second consideration is effectiveness. Is this transplantation actually effective? How long are its therapeutic effects sustained? And is it effective over the long term? The third consideration is mechanisms. What is the nature of graft behavior after implantation? Which behaviors are beneficial and which are harmful? What is the state of off-target differentiation? The fourth consideration is technology. How can graft survival be enhanced? What role does vascularization play? Only once these problems are fully addressed can hiPSC-derived β-like cells/islets be used clinically. These preclinical aspects cannot be directly studied in humans, so animal studies are a powerful tool with which to explore these aspects. However, available animal studies on this topic are thus far limited. Despite the limited number of included studies, the current study confirmed the hypoglycemic effects of transplantation. The effectiveness of both cell- and organoid-based transplantation increased over the four-week transplantation period. These findings may help with future animal studies and clinical transplantation. Thus, well-designed and insightful animal studies are anticipated.

5. Conclusions

This meta-analysis was performed to evaluate the hypoglycemic effects of hiPSC-based transplantation in animal models of diabetes. Current evidence suggests that β-like cell/islet transplantation contributes to reduced BG levels, with effectiveness tending to increase over the transplantation period. Improvements in glucose tolerance were also observed, indicating the enhanced insulin-related functional activity of the transplanted β-like cells/islets. Overall, this meta-analysis synthesizes existing preclinical evidence and it highlights the need for future well-designed studies to assess this approach's translational potential prior to clinical study.

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