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Stem cell therapy for erectile dysfunction: promise or reality? – a systematic review and meta-analysis of clinical trials

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Abstract

Background The outcomes of clinical trials on stem cell therapy (SCT) on erectile dysfunction (ED) treatment are promising but there is still no conclusive evidence regarding its efficacy. The aim of this meta-analysis is to compile studies that assess the effectiveness of SCT on ED to reach a more reliable conclusion.

Methods The meta-analysis was registered to PROSPERO (CRD42024540511). We utilized the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline to report the outcomes. Articles published from January 2000 to May 2024 were included for systematic review. We performed a systematic search using keywords: "stem cell" AND ("erectile dysfunction" OR "erectile function" OR "erection" OR "impotence").

Results We initially identified 2,013 studies in full publications or abstracts using the search terms. Eleven studies were included in systematic review and six of them were included in meta-analysis. Most studies included in systematic review reported improvements in erectile function following intracavernosal SCT. The meta-analysis revealed significant improvements at six months in international index of erectile function-5 (IIEF-5), international index of erectile function-erectile function domain) IIEF-EF, erectile hardness score (EHS), and peak systolic velocity (PSV) ($p < 0.05$). End-diastolic velocity (EDV) increased significantly at 3 months ($p = 0.031$) but not at six months ($p = 0.868$). Heterogeneity ranged from low to high ($I^2 = 0–71.2\%$). No significant publication bias was detected (Egger's test $p > 0.05$).

Conclusion Intracavernosal SCT may increase scores on the questionnaires evaluated compared to baseline at six months which currently represent the longest reported follow-up duration but comparative trials with longer follow-up periods are needed to draw more definitive conclusions and reveal long-term effect.

Keywords ED, Erectile dysfunction, Regenerative therapy, Stem cell

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Background

Penile erection is a complicated physiological process, involving integration of neural, vascular and endocrinologic pathways. It includes arterial dilatation, trabecular smooth muscle relaxation and activation of corporeal veno-occlusive mechanisms [1]. Erectile dysfunction (ED) is described as inability to ensure and sustain penile erection required for a satisfactory sexual intercourse [2]. ED may influence psychosocial health and have a major negative impact on the patients' and their sexual partners' quality of life [3]. ED etiology is multifactorial, with underlying vasculogenic, neurogenic, anatomic, hormonal, drug-induced and psychogenic mechanisms. Neurogenic and vasculogenic ED occur due to damage to the cavernous nerves and impaired blood flow to the cavernous bodies, respectively. Reversible and irreversible risk factors such as diabetes, obesity, dyslipidemia, hypertension, smoking, and aging, cardiovascular disease, and pelvic nerve injury contribute to the development and progression of ED [4].

The main principle of stem cell therapy (SCT) is the regenerative effect, to re-achieve normal functions of the tissues and organs. SCT has been in the spotlight of ED research along with many other medical fields utilizing its regenerative aspects. Preclinical studies on ED with different cell types shows promising results by induction of angiogenesis, increase in the expression and activity of endothelial mediators, activation of endothelial nitric oxide synthase (eNOS), increase in neuronal nitric oxide synthase (nNOS) and neurofilaments, preserving and growth of smooth muscle and prevention of cavernosal fibrosis. However, many of these benefits are mediated by paracrine signaling rather than long-term engraftment [5]. Driven by the results of these preclinical studies, clinical trials discussed on this present study evaluate the efficacy and safety of SCT in ED treatment.

Therefore, the aim of this systematic review and meta-analysis is to compile studies that assess the effectiveness of SCT in ED to reach a more consistent and reliable conclusion. To our best knowledge, this is the first meta-analysis focused exclusively on clinical trials of SCT for ED distinct from broader regenerative medicines reviews.

Methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to report the synthesis of data. The methodology was designed before the review of articles. The current meta-analysis was registered to PROSPERO (CRD42024540511).

Search strategy and information source

Articles were reviewed independently by two authors (SS and MD). The PubMed Central, Web of Science and Scopus databases were searched for articles published from January 2000 through May 2024. The final research was run on 21.05.2024. The language was restricted to English to facilitate the review of full articles. We performed a systematic search using keywords: "stem cell" AND ("erectile dysfunction" OR "erectile function" OR "erection" OR "impotence"). Medical Subject Headings (MeSH) terms were not formally applied, which may have limited search sensitivity. Reference lists were reviewed for further articles.

Study selection

Articles were reviewed independently by the 2 authors (SS and MD). Disagreements were solved by discussion. Inclusion criteria were (1) clinical trials; (2) with a population of adult men with all degrees of ED based on the; (3) with an intervention involving SCT intracavernosal injections; (4) reporting one or more of the outcomes of peak systolic velocity (PSV), end-diastolic velocity (EDV), IIEF, IIEF-5, IIEF-EF and erectile hardness score (EHS) with at least three-month follow-up period.

Exclusion criteria were; (1) SCT interventions with outcomes of values with median (because of insufficient number of trials to be able to perform a meta-analysis) (included in the systematic review); (3) SCT interventions in any way other than intracavernous (e.g., intravenous or transendocardial); (4) SCT interventions combined other treatment modalities (e.g., platelet rich plasma) (included in the systematic review); (5) intervention with a SCT-derived material (not SCT itself, e.g., stem cell-derived bioactive molecule) (6) short-term follow-up (with a follow-up period of < 3-month posttreatment); (7) incomplete outcome data (only reported the changes of point between pretreatment and posttreatment period or did not report on the primary outcomes of interest exactly) (included in the systematic review); and (8) reviews, case reports, and studies that continuous with each other and that were not written in English.

Data extraction

The extracted data for each study were as follows: first author's name, publication year, study design, arms, cause of ED, endpoints such as PSV, EDV, IIEF-5, IIEF, IIEF-EF, EHS, follow-up period, study and intervention size, stem cell type, administered number of stem cells and administration method. Comprehensive details regarding the study characteristics included in the systematic review and the meta-analysis are outlined in Table 1.

Quality assessment

We assessed the quality of manuscripts using the Newcastle–Ottowa scale (NOS) [12]. Among the 11 studies evaluated, the classification was good quality for two studies, fair for six studies and poor for three studies. Among the six studies included in the meta-analysis, the

Table 1 Characteristics of the studies included in the systematic review

Study	Study design	Arms	Age (years), mean ± SD or median (min-max)	Cause of ED	ED duration, mean ± SD or median (min-max)	Endpoint	Follow-up	Study size	Intervention size	Stem cell type	Number of stem cells/ml	Administration method
Alhefnawy et al. [6]	Pilot study	Single arm	52.3 ± 6.4	DM	NR	IIEF-EF, PSV, EDV	6 mo	10	10	BM-MSC	NR/10 ml	Unilateral ICI, single dose, no clamping
Fode et al. [7]	Phase 1	Single arm	61 (54–65)	Heterogeneous	36 (24–84) mo	IIEF, safety	6 mo	10	10	AD-MSC	NR/4 ml	Bileteral ICI, single dose, no clamping
Al Demour et al. [4]	Phase 1/ open label	Single arm	59.2 ± 8.4	DM	NR	IIEF-5, PSV, EDV, EHS, safety, tolerability	12 mo	22	22	WJ-MSC	20×10^6/4 ml	Bileteral ICI, two doses with 30 days interval, no clamping
Mirzaei et al. [8]	RCT/single blinded	Two arms	63.8 ± 7.4	DM	NR	IIEF-5, PSV, EDV, RI, safety	6 mo	20	10	OM-MSC	$50–60 \times 10^6$/2 ml	Bilateral ICI, single dose, clamping for 3 min
Koga et al. [9]	Phase 1/ open labe	Single arm	56 (31–79)	Heterogeneous	NR	IIEF-5, safety	8 wk	38	38	SHED-CM	10×10^6/2 ml	Bilateral ICI, 3–8 doses, loose clamping for 6 h
You et al. [10]	Phase 1/ open label	Single arm	62 ± 13	DM Post-RP	40.5 (2-112) mo	IIEF, PSV, RDV, RI, SEP, GAQ, safety	12 mo	10	10	BM-MSC	3×10^6/2 ml	Unilateral ICI, single dose, clamping for 30 min
Protogerou et al. [11]	Phase 1/ open label	Single arm	56.8 ± 6.7	Heterogeneous	NR	IIEF-5, PSV, EDV, safety	6 mo	5	5	AD-MSC	$9.5–51.4 \times 10^6$/2 ml	Unilateral ICI, single dose, clamping for 10 min
Haahr et al. [12]	Phase 1/ open label	Single arm	60.2 (46–69)	Post-RP	10.7 (6–15) mo	IIEF-5, EHS, safety	12 mo	21	21	AD-MSC	3.1×10^6/4 ml	Bileteral ICI, single dose, no clamping
Yiou et al. [13]	Phase 1–2/ open label	Single arm	59.9 ± 3.8 (stage two patients) 63.9 ± 4.4 (stage one patients)	Post-RP	26.3 ± 6.4 mo (stage two patients) 24.4 ± 9.8 mo (stage one patients)	IIEF-EF, EHS, safety	12 mo	15	15	BM-MNC	$2 \times 10^7–10^9$/NR	Unilateral ICI, single dose, no clamping
Levy et al. [14]	Phase 1–2/ open label	Single arm	61	Heterogeneous	NR	IIEF, PSV, EDV, safety	6 mo	8	8	PM-MSC	NR	Bileteral ICI, single dose, no clamping
Bahk et al. [15]	Phase 1/ single blinded	Two arms	69.5 (57–87)	DM	> 1 year	IIEF (partial questions), SEP, GAQ, safety	11 mo	10	7	UC-MSC	15×10^6/NR	Bileteral ICI, single dose, clamping for 30 min

ED Erectile Dysfunction, *DM* Diabetes Mellitus, *IIEF-EF* International Index of Erectile Function-Erectile Function Domain, *IIEF* International Index of Erectile Function, *IIEF-5* 5-item International Index of Erectile Function, *PSV* Peak Systolic Velocity, *EDV* End Diastolic Velocity, *EHS* Erection Hardness Score, *RI* Resistive Index, *SEP* Sexual Encounter Profile, *GAQ* Global Assessment Question, *BM-MSC* Bone Marrow-Derived Mesenchimal Stem Cell, *AD-MSC* Adipose Tissue-Derived Stem Cell, *WJ-MSC* Wharton Jelly-Derived Mesenchymal Stem Cell, *OM-MSC* Oral Mucosa-Derived Stem Cell, *SHED-CM* Dental Pulp Exfoliated Deciduous Stem Cell, *BM-MNC* Bone Marrow Mononucleated Cells, *PM-MSC* Placental Matrix-Derived Stem Cell, *UC-MSC* Umblical Cord Blood-Derived Stem Cell, *ICI* Intracavernosal Injection, *NR* Not-reported

classification was good quality for one study and fair for five studies. The details and calculated total scores are demonstrated in Table 2. In addition to the NOS applied to non-randomized studies, we assessed the single randomized controlled trial [8] using the Cochrane Risk of Bias 2.0 (RoB 2) tool. The study was determined to be at low risk of bias across all domains, including randomization, outcome measurement, and reporting.

Statistical analysis

We performed the statistical analysis using Comprehensive Meta-analysis Version 4 (Biostat, Englewood, NJ, USA). The forest plots were produced from the studies comparing the baseline and third-month and baseline and sixth-month values of PSV, EDV, IIEF-5, IIEF, IIEF scores and EHS. We determined the effect size as the standardized mean difference (SMD) with confidence intervals (CI). We evaluated the studies' heterogeneity using Cochran's Q and I^2 statistic tests. A random effect model was used if evident heterogeneity and inconsistency were available across the studies. Otherwise, a fixed effect model was used. I^2 values of 25–49%, 50–74%, and 75% or greater were considered as low, moderate, and high heterogeneity, respectively. We assessed publication bias using the Egger test. Egger's test was only performed for outcomes with at least three studies and is considered unreliable for fewer than ten studies due to low power. The p-value of less than 0.05 was considered statistically significant.

Results

Study selection and characteristics

A total of 2.013 records were identified through the search strategy, and after screening and applying eligibility criteria, 11 studies were included in the systematic review and six in the meta-analysis. Detailed information regarding the literature search is depicted in Fig. 1.

The six studies [4, 6, 9–11, 13, 15] included in meta-analysis encompassed a total of 75 patients. Four of them were phase 1–2/open label, single arm studies, one study was single arm pilot study and one study was randomized-controled, single blinded study. These studies were published between 2016 and 2023. The characteristics of studies included in systematic review and meta-analysis are detailed in Table 1.

Changes in PSV

The comparison between baseline and third-month PSV

Three studies [4, 13, 15] evaluated the baseline and post-therapy third-month PSV. The pooled SMD was 0.63 (0.28–0.98), indicating a medium effect size ($p < 0.0001$). No evident heterogeneity was detected ($p = 0.15$; $Q = 3.72$; $I^2 = 46.31$). No publication bias was detected (p-value for Egger test = 0.66) (Fig. 2A).

The comparison between baseline and sixth-month PSV

Three studies [6, 13, 15] evaluated the baseline and post-therapy sixth-month PSV. The pooled SMD was 1.2 (0.23–2.19), indicating a large effect size ($p = 0.015$). Moderate heterogeneity was detected ($p = 0.03$; $Q = 6.96$; $I^2 = 71.24$). No publication bias was detected (p-value for Egger test = 0.09) (Fig. 2B).

Changes in EDV

The comparison between baseline and third-month EDV

Three studies [4, 13, 15] evaluated the baseline and post-therapy third-month EDV. The pooled SMD was 0.36 (0.03–0.68), indicating a small effect size ($p = 0.031$). No evident heterogeneity was detected ($p = 0.28$; $Q = 2.57$; $I^2 = 22.11$). No publication bias was detected (p-value for Egger test = 0.27) (Fig. 3A).

The comparison between baseline and sixth-month EDV

Three studies [6, 13, 15] evaluated the baseline and post-therapy sixth-month EDV. The pooled SMD was 0.06 (–0.67 to 0.79), which is not statistically significant ($p = 0.868$), indicating negligible effect on EDV at 6 months. Moderate heterogeneity was detected ($p = 0.03$; $Q = 6.76$; $I^2 = 70.40$). No publication bias was detected (p-value for Egger test = 0.65) (Fig. 3B).

Table 2 The Newcastle Ottowa scale for quality assessment of studies included meta-analysis

Author (year)	Selection	Comparability	Outcome	Total	Quality
Mirzaei et al. [8]	****	*	***	8 *	Good
Al Demour et al. [4]	***		***	6 *	Fair
Alhefnawy et al. [6]	***		***	6*	Fair
Levy et al. [14]	***		***	6 *	Fair
Yiou et al. [13]	****		***	7 *	Fair
You et al. [10]	****		***	7 *	Fair
Fode et al. [7]	***		**	5*	Poor
Koga et al. [9]	***		**	5*	Poor
Protogerou et al. [11]	***		**	5*	Poor
Haahr et al. [12]	****		**	6*	Fair
Bahk et al. [15]	***	*	**	6*	Good

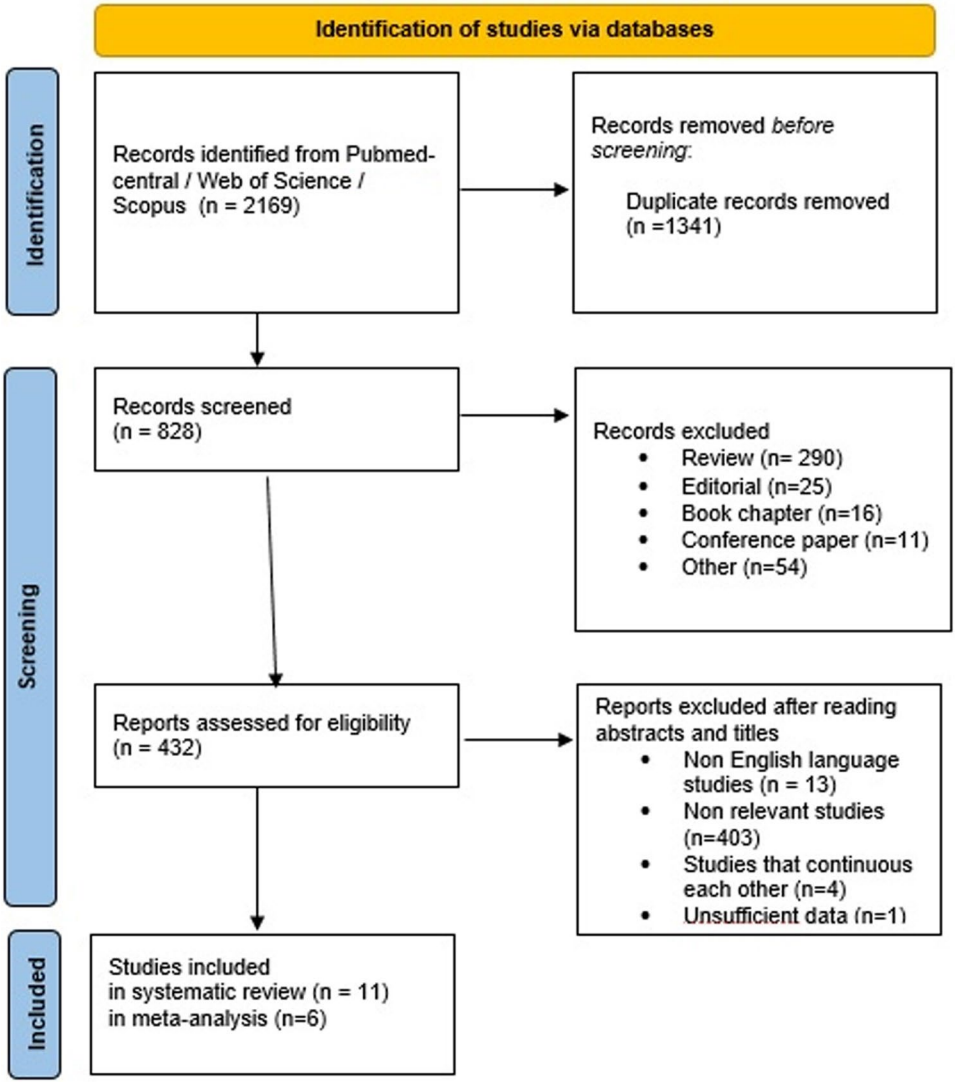


Fig. 1 PRISMA flowchart—study selection with inclusion and exclusion criteria of reviewed studies. PRISMA, Preferred reporting items for systematic reviews and meta-analysis

Changes in IIEF-5 score

The comparison between baseline and third-month IIEF-5 score

Two studies [4, 13] evaluated the baseline and post-therapy third-month IIEF-5 scores. The pooled SMD was 1.05 (0.61–1.49), indicating a large effect size ($p < 0.0001$). Moderate heterogeneity was detected although the p-value for Cochran's Q test was not statistically significant ($p = 0.16$; $Q = 2.01$; $I^2 = 50.16$). A publication bias assessment was not done, as only two studies were included (Fig. 4A).

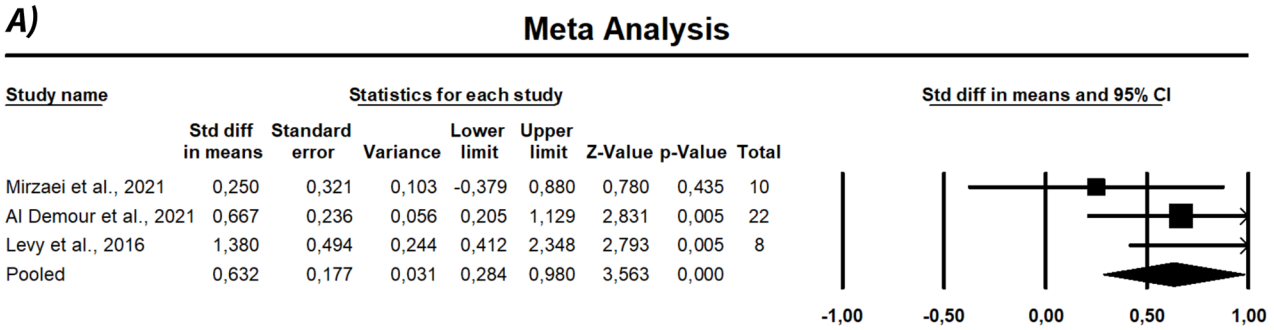
The comparison between baseline and sixth-month IIEF-5 score

Two studies [4, 13] evaluated the baseline and post-therapy sixth-month IIEF-5 scores. The pooled SMD was 1.23 (0.77–1.70), indicating a large effect size ($p < 0.0001$). Moderate heterogeneity was detected although the p-value for Cochran's Q test was not statistically significant ($p = 0.15$; $Q = 2.07$; $I^2 = 51.59$). A publication bias assessment was not done, as only two studies were included (Fig. 4B).

Changes in IIEF score

The comparison between baseline and third-month IIEF score

Two studies [9, 15] evaluated the baseline and post-therapy sixth-month IIEF scores. The pooled SMD was −0.11 (−0.58 to 0.36), which is not statistically significant ($p = 0.647$), suggesting no observable change in IIEF at 3 months. No evident heterogeneity was detected ($p = 0.42$; $Q = 0.64$; $I^2 < 0.0001$). A publication bias assessment was not done, as only two studies were included (Fig. 5A).



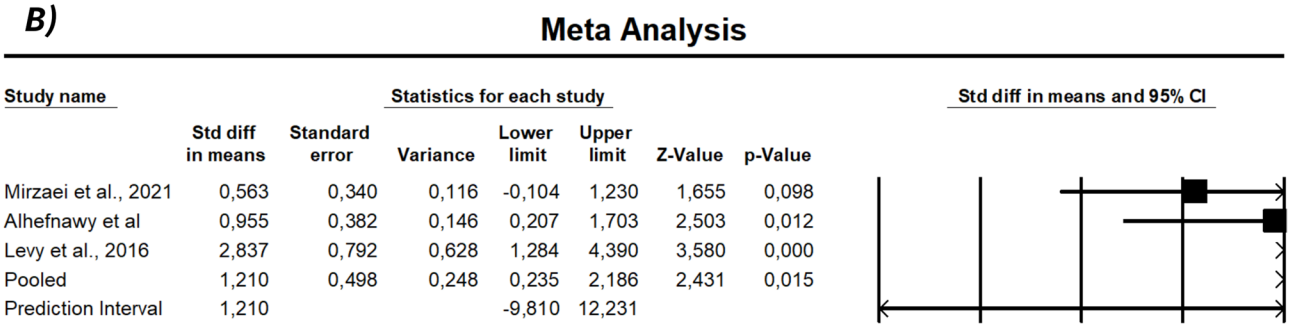
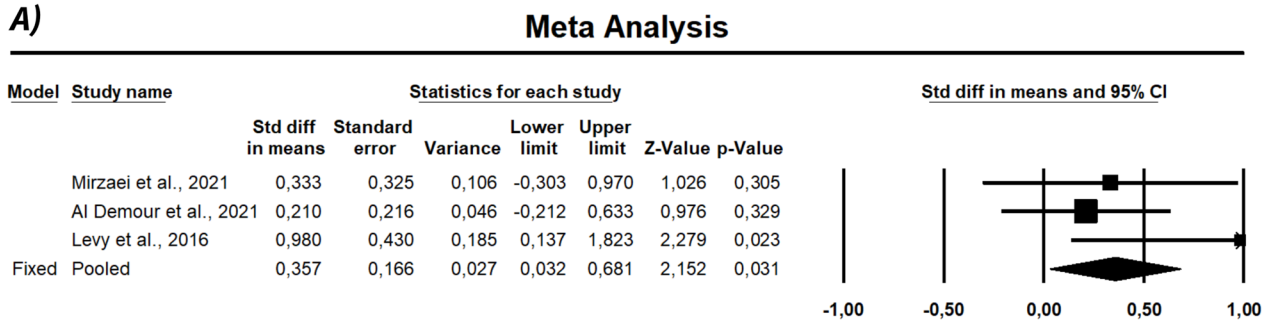


Fig. 2 The forest plots of the studies comparing: **A** baseline and third-month PSV value (p value for heterogeneity: 0.15; Q = 3.72; $I^2 = 46.31$) (**B**) baseline and sixth-month PSV value (*p* value for heterogeneity: 0.03; Q = 6.96; $I^2 = 71.24$)



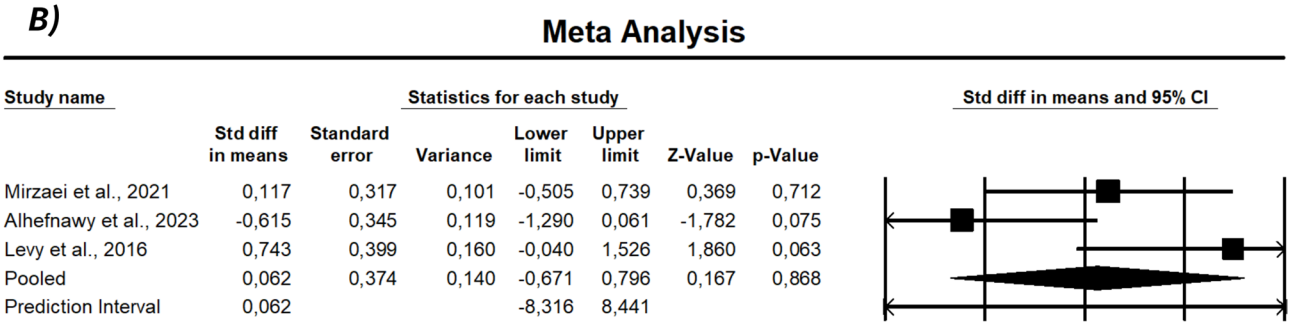


Fig. 3 The forest plots of the studies comparing: **A** baseline and third-month EDV value (*p* value for heterogeneity: 0.28; Q = 2.57; $I^2 = 22.11$) (**B**) baseline and sixth-month EDV value (*p* value for heterogeneity: 0.03; Q = 6.76; $I^2 = 70.40$)

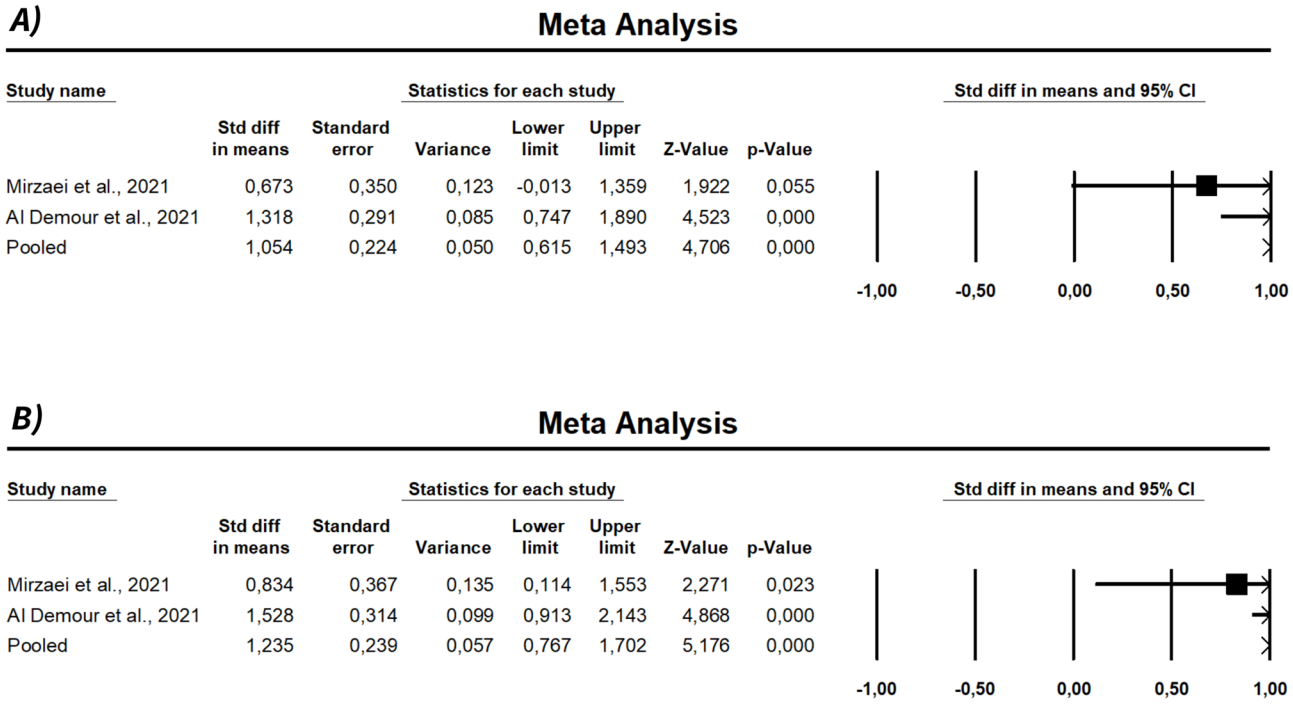


Fig. 4 The forest plots of the studies comparing: **A** baseline and third-month IIEF-5 value (*p* value for heterogeneity: 0.157; Q = 2.01; $I^2 = 50.16$) (**B**) baseline and sixth-month IIEF-5 value (*p* value for heterogeneity: 0.151; Q = 2.07; $I^2 = 51.59$)

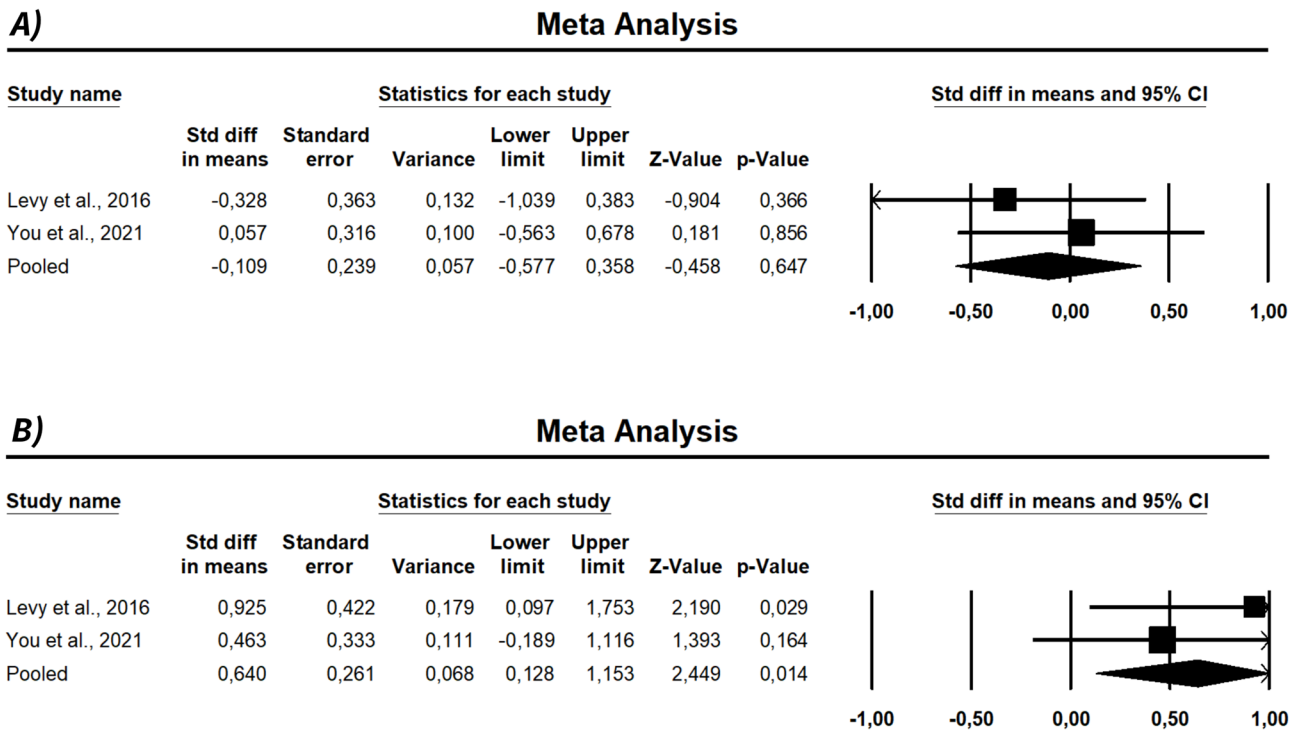


Fig. 5 The forest plots of the studies comparing: **A** baseline and third-month IIEF value (*p* value for heterogeneity: 0.424; Q = 0.64; $I^2 < 0.0001$) (**B**) baseline and sixth-month IIEF value (*p* value for heterogeneity: 0.391; Q = 0.74; $I^2 < 0.0001$)

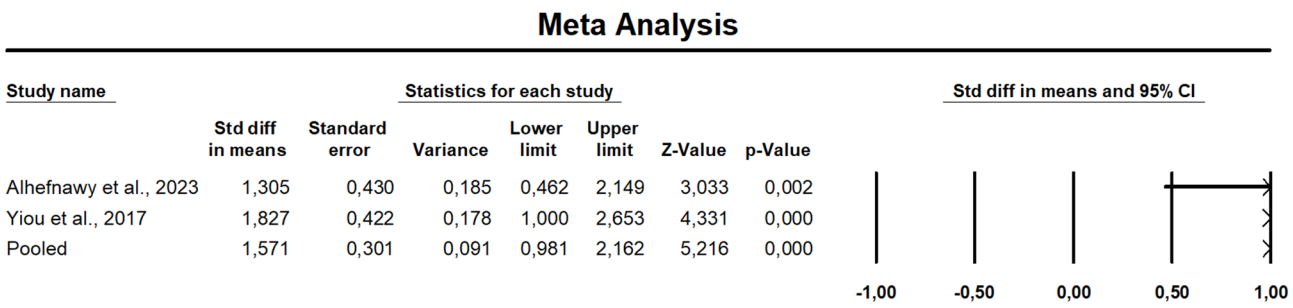
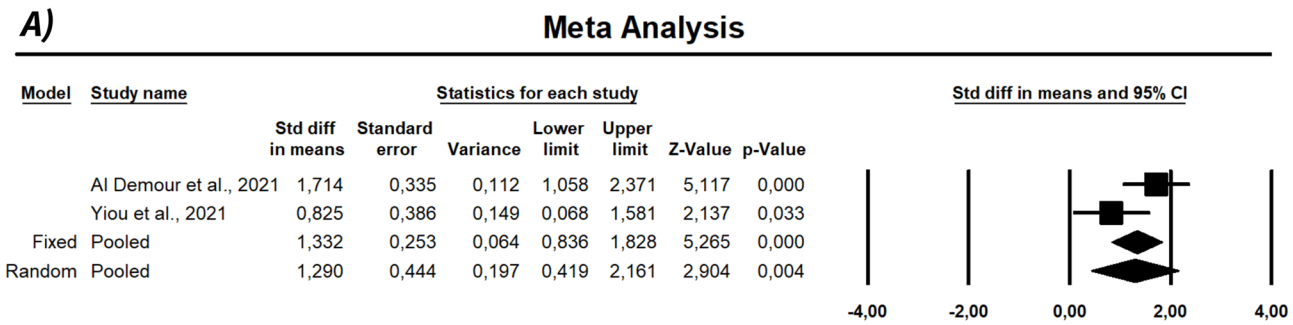


Fig. 6 The forest plots of the studies comparing baseline and sixth-month IIEF-EF value (*p* value for heterogeneity: 0.387; Q = 0.75; $I^2 < 0.0001$)



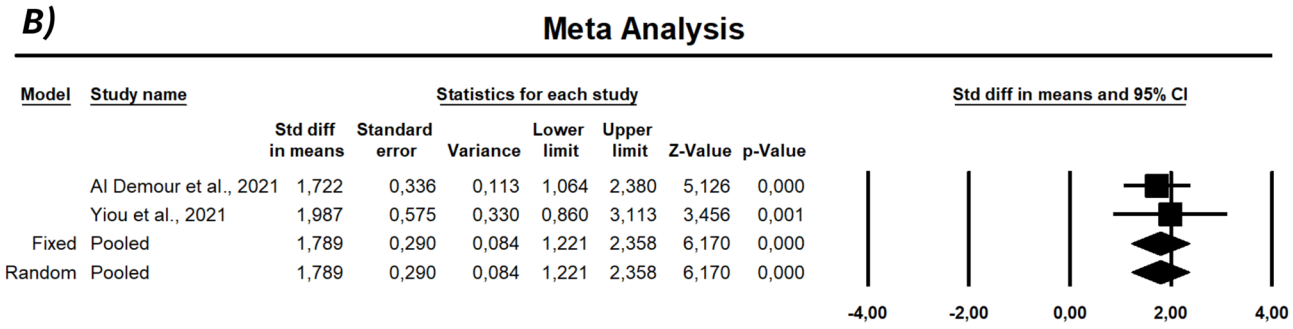


Fig. 7 The forest plots of the studies comparing: **A** baseline and third-month EHS value (p value for heterogeneity: 0.08; Q = 3.03; $I^2 = 66.99$) (**B**) baseline and sixth-month EHS value (*p* value for heterogeneity: 0.69; Q = 0.15; $I^2 < 0.0001$)

The comparison between baseline and sixth-month IIEF score

Two studies [9, 15] evaluated the baseline and post-therapy sixth-month IIEF scores. The pooled SMD was 0.64 (0.13–1.15), indicating a medium effect size ($p = 0.014$). No evident heterogeneity was detected ($p = 0.39$; Q = 0.74; $I^2 < 0.0001$). A publication bias assessment was not done, as only two studies were included (Fig. 5B).

Changes in IIEF-EF score

The comparison between baseline and sixth-month IIEF-EF score

Two studies [6, 9] evaluated the baseline and post-therapy sixth-month IIEF-EF scores. The pooled SMD was 1.57 (0.98–2.16), indicating a large effect size ($p < 0.0001$). No evident heterogeneity was detected ($p = 0.39$; Q = 0.75; $I^2 < 0.0001$). A publication bias assessment was not done, as only two studies were included (Fig. 6).

Changes in EHS

The comparison between baseline and third-month EHS

Two studies [4, 11] evaluated the baseline and post-therapy third-month EHS. The pooled SMD was 1.33 (0.83–1.82), indicating a large effect size ($p < 0.0001$). Moderate heterogeneity was detected ($p = 0.08$; Q = 3.03; $I^2 = 66.99$). A publication bias assessment was not done, as only two studies were included (Fig. 7A).

The comparison between baseline and sixth-month EHS

Two studies [4, 11] evaluated the baseline and post-therapy sixth-month EHS. The pooled SMD was 1.78

(1.22–2.35), indicating a large effect size ($p < 0.0001$). No evident heterogeneity was detected ($p = 0.69$; $Q = 0.15$; $I^2 < 0.0001$). A publication bias assessment was not done, as only two studies were included (Fig. 7B).

Qualitative synthesis of studies not included in meta-analysis

In addition to the six studies included in the meta-analysis, five studies were included in the systematic review but excluded from quantitative analysis due to non-extractable outcome data (e.g., medians, lack of standard deviations), alternative administration methods, or reporting outcomes incompatible with meta-analytic pooling. A qualitative assessment of these studies revealed that their findings were generally consistent with the meta-analysis results, demonstrating favorable outcomes following SCT.

Haahr et al. conducted a phase 1 trial with 21 post-prostatectomy ED patients who received a single intracavernosal injection of autologous adipose-derived mesenchymal stem cells (AD-MSCs). IIEF-5 scores improved from a median of 6 to 11 at 6 months, before slightly decreasing to 9 at 12 months in the continent subgroup, suggesting transient benefits of SCT in this population [12].

Koga et al. administered dental pulp exfoliated deciduous stem cells (SHED-CM) intracavernosally with loose penile constriction. They observed increased IIEF-5 scores and improved penile hemodynamics, particularly in younger patients with fewer comorbidities, reinforcing the potential regenerative effect of stem cell-based approaches [9].

Bahk et al. delivered umbilical cord blood stem cells to seven diabetic men with refractory ED. Three patients experienced morning erections within one month; however, long-term effects were limited, with only one patient retaining coital function at 11 months. These findings suggest early but possibly temporary benefits [15].

Fode et al. conducted a small feasibility study in which autologous AD-MSCs were injected in a same-day, minimally invasive protocol. Although this study lacked formal quantitative erectile function outcomes such as IIEF scores, the investigators reported subjective improvement in erectile function in some patients and confirmed safety and procedural feasibility, supporting SCT as a tolerable treatment in the outpatient setting [7].

Protogerou et al. evaluated the combination of SCT with platelet lysate plasma in a pilot study. At the 6-month follow-up, patients exhibited improved IIEF-5 and EHS scores, indicating a potential synergistic effect; however, due to the combination therapy and lack of standard deviation data, this study could not be included in the meta-analysis [11].

Taken together, these studies—though methodologically heterogeneous—demonstrate a similar directionality of effect as the studies included in the meta-analysis. Most showed six months improvements in erectile function parameters, particularly IIEF-related scores and PSV, supporting the therapeutic potential of SCT in ED.

Discussion

Clinical trials included in this meta-analysis evaluating the effectiveness of SCT utilize validated questionnaires IIEF scores, EHS, and penile doppler ultrasonography parameters (PSV and EDV). According to the results of this meta-analysis, SCT was effective in ED treatment by increasing mean IIEF scores and mean PSV value. The improvement in IIEF-5 score at six months showed a large effect size (SMD: 1.23, 95% CI: 0.77 to 1.70), indicating a likely 4–6 point increase — a clinically meaningful gain that could shift patients from moderate to mild ED [16]. Although EDV slightly increased at 3 months suggesting a temporary deterioration in veno-occlusive function, it increased again by 6 months as not showing significant differences from the baseline values. These results demonstrate the potential efficacy of SCT for treating ED.

It was shown in preclinical studies that multiple regenerative mechanisms, including the induction of angiogenesis, enhancement of eNOS and nNOS expression, suppression of apoptosis, and prevention of cavernosal fibrosis are largely mediated via paracrine signaling, rather than permanent engraftment of stem cells. n a review by Chung et al., SCT was shown to activate signaling pathways that enhance endothelial and neuronal recovery and improve smooth muscle content [5]. Thorve et al. outlined how chronic diabetes induces endothelial and smooth muscle apoptosis, which SCT may reverse [17]. Dashwood et al. identified reduced nNOS expression as a key factor in diabetic ED, which SCT could potentially restore [18]. These mechanistic findings support the clinical efficacy observed in our meta-analysis and highlight the biological plausibility of SCT as a therapeutic option for ED.

ED prevalence in diabetic patients is 50–70% and the risk for ED development is 3 times higher than normal population [19, 20]. ED pathogenesis of diabetic patients involves vascular endothelial damage, diminished smooth muscle volume, neural degeneration, fibrosis, and testicular insufficiency [21]. Long term diabetes mellitus (DM) results in apoptosis and dysfunction in corporal endothelium and smooth muscle, lowers nitric oxide (NO) levels and increases oxidative stress in cavernous tissue [18]. Diabetic patients benefit less from PDE5 inhibitors [22]. This leads to a need for more effective and durable treatment choices. In a prospective phase 1/2, open-label, single-arm, and single-center trial by Al Demour et al., 22 ED patients with a mean 11-year DM duration were recruited. These patients experienced an

average increase of 4.5 cm/s in basal PSV at 3 months following intracavernosal stem cell injection. IIEF-5 scores were increased by 5.1 points compared to baseline values at sixth-month. Average IIEF-5 scores decreased by 3.3 points at 12 months when compared to the sixth-month evaluation, but a statistically significant increase was still persistent when compared to baseline values [4]. Alhernawy et al. applied SCT to 10 diabetic ED patients with BM-MSC. Assessment at the sixth-month revealed an increase in IIEF-EF scores from 12.7 to 19.2, and an increase in average PSV from 25 cm/s to 40.9 cm/s. Average EDV regressed to 0.9 cm/s from 3.9 cm/s [6]. Bahk et al. recruited 7 diabetic, medical therapy-resistent ED patients without morning erections, and at the first-month after intracavernosal SCT, 3 patients experienced morning erections. 2 patients achieved penetration with PDE5 inhibitors at 5 months. However, at the end of the 11-month follow-up period, 3 patients went back to non-erectile status, 3 patients had poor erections and only 1 patient had erections sufficient for coitus [8]. These studies show the efficacy of SCT in diabetic ED patients. Nevertheless, the diminished effect at 6- and 12-months during follow-up demonstrates the possibility of a short-term benefit in erectile function. Patients with longstanding diabetes may have more fibrotic tissue and microvascular disease, reducing responsiveness to regenerative therapies.

Importantly, a recent 24-month follow-up study by Al Demour et al. reported sustained improvements in IIEF-5 scores in diabetic men receiving two intracavernosal injections of autologous BM-MSCs, without major adverse events [23]. This longer-term open-label phase 2 trial builds on their earlier phase 1 trial, which demonstrated the short-term safety and potential efficacy of the same protocol [24]. Together, these studies provide rare insights into the durability and safety of SCT in diabetic ED, highlighting the importance of repeated dosing and extended follow-up for evaluating regenerative therapies.

Twenty diabetic ED patients unresponsive to medical therapy were recruited in a well-designed, randomized, controlled, single-blind clinical trial by Mirzaei et al., and these patients were administered with a single injection of both corpora cavernosa with a penile clamp placed at the bottom of the penis for 3 min. The intervention group of 10 patients were injected with 2 ml $5\text{-}6 \times 10^7$ Oral mucosa-derived MSCs (OM-MSC) and the control group of 10 patients were injected with 2 ml saline. IIEF-5 scores at sixth-month showed an increase of an average of 3.4 points (from 7.2 to 10.6, $p = 0.01$) in the intervention group, and an average of 0.1 points (from 7.2 to 7.3, $p = 0.87$) in the control group. PSV values of the intervention group increased for an average of 2 cm/s (from 8.26 cm/s to 10.22 cm/s, $p = 0.01$), and no change was detected in the control group (from 8.21 cm/s to 8.2 cm/s, $p = 0.11$). EDV values of both groups did not show statistically significant differences ($p = 0.36$, $p = 0.49$, respectively). No adverse effects were reported at the end of the study [13].

The clinical trial by Haahr et al. involved 21 postprostatectomy ED patients in two groups. These patients were intracorporeally administered with a single average dose of 3.1×10^6 AD-MSC. One patient group with a median baseline IIEF-5 score of 6, had a stable IIEF-5 score at the first month, and this score raised to 11 at 6 months, and dropped back to 9 at 12 months. The other group did not experience an increase in the IIEF-5 scores [7]. Yiou et al. recruited 9 patients with postprostatectomy ED unresponsive to pharmacotherapy. A significant increase in the first month average IIEF-EF scores was identified after injection of intracavernosal bone marrow mononucleated cells. An increase of 11.3 points was detected until 6 months, and in the follow-up until 12 months and later, IIEF-EF scores dropped by 3.1 points. A similar recovery pattern was seen during maximal pharmacotherapy use, but after cessation of maximal pharmacotherapy, EHS did not significantly change [11]. Studies involving post-radical prostatectomy patients address a primarily neurogenic etiology, with damage to the cavernous nerves as a key mechanism. In such cases, SCT may exert effects via neurotrophic and anti-inflammatory pathways [7, 11].

Among the clinical trials discussed in the current systematic review, 4 clinical trials reported no adverse effects related to SCT [8, 9, 11, 13]. 4 clinical trials reported minor side effects such as minor discomfort, irridation and minor pain, redness, swelling, local reaction, and itching at the injection site [7, 12, 15, 25]. Along with these, in the clinical trial where Al Demour et al. administered 2 intracavernosal injections of 20×10^6 WJ-MSCs with a 30-day interval, 2 patients had minimal redness and swelling at the base of the penis and 1 patient developed a minimal fibrous plaque on the dorsal aspect of the penis without curvature, 3 months after the second injection. Post-injection VAS scores were also calculated in this study, to evaluate tolerability of injections. VAS score was reported to range from 0 to 3 [4]. Although the included trials reported only mild adverse events, the small sample sizes and short-term follow-up limit conclusions about long-term safety. Rare but serious complications, such as fibrosis, immune reactions, or tumorigenesis, may not emerge until larger, longer studies are conducted.

The patients included in the studies were generally adult men with moderate-to-severe erectile dysfunction, many of whom were unresponsive to first-line oral PDE5 inhibitors or intracavernosal injection therapy [4, 7, 11, 13]. Several trials specifically enrolled patients with diabetes mellitus, a known risk factor for ED and poor

response to standard treatments [4, 6, 8]. Others, such as the trials by Haahr et al. and Yiou et al., focused on men with post-prostatectomy ED, who often have a neurogenic component to their dysfunction [7, 11]. These characteristics—treatment-refractory status, presence of diabetes, and post-surgical etiology—may limit the generalizability of the findings to broader ED populations, particularly those with mild, psychogenic, or more reversible causes of ED.

The variation in treatment effect across studies may be attributed to differences in stem cell source, dosage, injection protocols, cell survival and patient populations. For example, diabetic patients often exhibit advanced endothelial dysfunction, cavernosal fibrosis, and oxidative stress — conditions that may limit stem cell homing, survival, and angiogenic potential. In contrast, younger patients or those with post-prostatectomy ED may have more recoverable neural or vascular pathways, albeit with nerve injury as a complicating factor. The observed decline in efficacy over time, noted in several studies after 6–12 months, may be related to limited stem cell survival or transient paracrine signaling rather than durable engraftment. Most studies used a single administration, and it is plausible that repeated injections or supportive co-therapies (e.g., low-intensity shockwave therapy, pharmacologic enhancers) could help sustain functional gains. Further trials are needed to explore optimal dosing schedules, repeat injections, and cell delivery scaffolds to improve engraftment and durability. Additionally, the timing of follow-up assessments (ranging from 3 to 12 months) may influence whether short-term benefits are captured or missed.

The studies included in this meta-analysis are limited by small sample sizes, lack of control groups, and heterogeneous patient populations. It can introduce potentially selection bias since our meta-analysis required only means and standard deviations. Lack of control groups prevents rulling out placebo effect. While a random effects model was applied to account for statistical heterogeneity, notable clinical heterogeneity was present across the studies in terms of types of stem cells, administration protocols, number of cells administered and number of injections. Only two clinical trials were able to be included in the meta-analysis to evaluate the effectiveness of SCT on IIEF, IIEF-5, IIEF-EF and EHS because there were few trials available to be able to perform a meta-analysis. Objective assessment methods like PSV and EDV were utilized in a part of the studies. Also, there were differences in follow-up periods. These differences may limit the comparability of studies, and the pooled estimates should therefore be interpreted with caution. In addition, this meta-analysis only included published, English-language articles from peer-reviewed journals and did not include clinical trial registries or grey literature (e.g., conference abstracts). As a result, there is a potential risk of publication bias, which may limit the comprehensiveness of the findings. While potential sources of heterogeneity may include differences in stem cell type, administration protocols, or patient characteristics (e.g., diabetic vs. post-prostatectomy), sensitivity and subgroup analyses were not performed due to the small number of studies included per outcome (typically only two or three). Although moderate to high heterogeneity was detected in some comparisons, further analysis was not feasible without introducing statistical bias or overinterpretation.

Finally, although our study has demonstrated statistically significant improvement in erectile function after SCT, a very limited number of studies were included in the meta-analysis and the heterogeneity restricts our ability to make conclusive interpretations regarding clinical significance. SCT for ED is not yet ready for widespread clinical use. Most trials are early-phase, with limited standardization in cell type, dose, and delivery methods. Additionally, regulatory, ethical, and cost considerations remain unresolved. SCT should currently be offered only in the context of clinical trials.

Conclusion

This meta-analysis stated that intracavernosal SCT may increase scores on the questionnaires and PSV values evaluated compared to baseline in short-term. There is a need for larger, well-designed randomized controlled trials with longer follow-up periods to draw more definitive conclusions. However, our findings provide the pooled evidence supporting short-term efficacy, highlighting both promise and the gaps requiring future research.

Abbreviations

SCT	Stem cell therapy
ED	Erectile dysfunction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IIEF-5	International index of erectile function-5
IIEF-EF	International index of erectile function-erectile function
EHS	Erectile hardness score
PSV	Peak systolic velocity
EDV	End-diastolic velocity
eNOS	Endothelial nitric oxide synthase
nNOS	Neuronal nitric oxide synthase
NOS	Newcastle–Ottowa scale
SMD	Standardized mean difference
CI	Confidence intervals
PDE5	Phosphodiesterase 5
MSCs	Mesenchymal stem cells
AD-MSCs	Adipose-derived MSCs
BM-MSCs	Bone marrow-derived MSCs
WJ-MSCs	Wharton's Jelly-derived MSCs
OM-MSCs	Oral mucosa-derived MSCs
SHED-CM	Dental pulp exfoliated deciduous stem cells
SVF	Stromal vascular fraction
DM	Diabetes mellitus
NO	Nitric oxide

PROSPERO number
The current meta-analysis was registered to PROSPERO (CRD42024540511).

Code availability
Not applicable.

Authors' contributions
Conceptualization: SS, AHS, HB, MD. Data curation: SS, HG, MD. Formal analysis: SS, AHS, HG, AJR, HB. Funding acquisition: MD, AK. Investigation: HG. Methodology: SS, MD, HB. Project administration: SS, AK. Resources: HB, MD. Software: HG, AJR. Supervision: AK, MD. Validation: AK, MD. Visualization: HG, HB. Writing – original draft: SS, MD. Writing – review & editing: SS, MD, AK.

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Declarations

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