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High-activity placenta-derived mesenchymal stem cells combined with low-intensity extracorporeal shock wave therapy for diabetic erectile dysfunction: a prospective randomized controlled trial

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Abstract

Objective To evaluate the efficacy and safety of high-activity placenta-derived mesenchymal stem cells (hPMSCs) in combination with low-intensity extracorporeal shock wave therapy (LI-ESWT) for the treatment of diabetic erectile dysfunction (ED).

Methods This prospective, randomized, controlled clinical trial enrolled 33 patients with refractory diabetic ED. Participants were randomly assigned in a 1:1:1 ratio to one of three groups: the hPMSCs group, the LI-ESWT group, or the combined therapy group (H + L). All subjects discontinued ED medications for at least two weeks prior to receiving the intervention. Treatment efficacy was assessed at baseline and at 1,3 and 6 months post-intervention using the International Index of Erectile Function – Erectile Function (IIEF-EF), Erection Hardness Score (EHS), Sexual Encounter Profile (SEP-2/SEP-3), and Rigiscan parameters, with safety outcomes monitored concurrently.

Results At the 6-month follow-up, the combined therapy group demonstrated significantly superior outcomes compared to the individual hPMSCs and LI-ESWT groups. Specifically, total erection time reached 22.20 (15.20, 30.25) minutes ($p = 0.001$) and full erection time reached 11.90 (11.55, 12.35) minutes ($p = 0.004$) in the combined group. Moreover, EHS scores improved markedly, with 70% of patients in the combined group achieving an EHS > 2 at 6 months ($p = 0.045$). No severe adverse events were observed in any group; any local mild pain resolved within one week.

Conclusion The combination of high-activity hPMSCs and LI-ESWT appears to be a safe and effective strategy for improving erectile function in patients with diabetic ED, demonstrating a synergistic effect in prolonging erection

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duration and enhancing penile hardness. This combined therapeutic approach represents a promising new option for the clinical management of diabetic ED, warranting further validation in larger, multi-center studies to confirm its long-term efficacy and safety.

Keywords Erectile dysfunction, Low-Intensity extracorporeal shock wave, hPMSCs

Introduction

Erectile dysfunction (ED) is a common condition in which men are unable to achieve or maintain an erection sufficient for satisfactory sexual intercourse. Approximately 2.5–3% of men develop ED annually (25–30 cases per 1,000 person-years), and 20–30% of adult males experience at least one SD event [1]. Diabetic ED significantly impairs psychological well-being, interpersonal relationships, and overall quality of life. Studies indicate that ED is strongly associated with depression, anxiety, and reduced self-esteem in diabetic patients, which may exacerbate metabolic dysregulation and complicate diabetes management. Addressing ED is therefore integral to holistic patient care [2]. The etiology of erectile dysfunction (ED) is multifactorial, involving both non-modifiable and modifiable risk factors. Established contributors include advanced age [3], dyslipidemia [4], hypertension [5], cardiovascular diseases [6], and physical inactivity [7]. Additional pathogenic factors encompass neurogenic disorders, hypogonadism, and iatrogenic causes [8]. Among these, arterial insufficiency and veno-occlusive dysfunction represent the most prevalent pathophysiological mechanisms [9]. In particular, patients with diabetes experience a markedly higher prevalence of ED due to chronic hyperglycemia-induced microvascular damage, neuropathy, and endocrine dysfunction [10].

Moreover, the management of diabetic erectile dysfunction (DED) remains clinically challenging, primarily due to diabetes-induced pathological alterations in cavernous tissues, including structural and functional impairments of smooth muscle cells, endothelial dysfunction, and neural degeneration [11]. Conventional treatment modalities for ED—including oral phosphodiesterase-5 (PDE-5) inhibitors, intracavernosal injections, and vacuum erection devices—may provide temporary symptomatic relief but generally fail to reverse the underlying pathological alterations in the corpora cavernosa. These pathological changes collectively contribute to the suboptimal response rates to phosphodiesterase type 5 inhibitors (PDE5i) [12]. Notably, a subset of patients demonstrates either pharmacotherapeutic resistance or adverse drug reactions, which emphasizes the urgent requirement for novel treatment paradigms featuring both regenerative potential and long-term safety profiles. Given the limitations of conventional symptomatic treatments in addressing the underlying pathophysiology, regenerative approaches targeting tissue repair have gained increasing attention.

Simultaneously, low-intensity extracorporeal shock wave therapy (LI-ESWT) has emerged as an innovative physical therapy that utilizes mechanical stimulation to induce local cytokine release and activate endogenous stem and endothelial cells, thus promoting neovascularization and neural regeneration. However, when applied as a monotherapy, LI-ESWT may yield limited and transient benefits, particularly in patients with diabetic ED, where its efficacy often falls short of clinical expectations.

In recent years, mesenchymal stem cells (MSCs) have emerged as a promising area of regenerative medicine due to their multipotent differentiation capabilities, robust secretion of paracrine factors, and low immunogenicity [13]. Placenta-derived MSCs (hPMSCs) are particularly attractive because of their abundant availability, relatively simple isolation procedures, high differentiation potential, and favorable safety profile [14, 15]. In the context of ED, MSCs have been shown to secrete vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and other cytokines that promote angiogenesis, nerve regeneration, and exert anti-inflammatory effects, thereby improving erectile function [16]. Recent studies have demonstrated that human umbilical cord mesenchymal stem cells (hUC-MSCs) can effectively restore erectile function in diabetic rats through multiple mechanisms, including TLR4 inhibition, reduction of cavernous fibrosis, and upregulation of VEGF and eNOS expression [17]. In parallel, transplantation of ADSCs-derived mitochondria (ADSCs-mito) has shown comparable efficacy to ADSCs therapy in ameliorating calcineurin inhibitor-induced erectile dysfunction (CNI-ED) [18]. The therapeutic effects of ADSCs-mito are potentially mediated through antioxidative stress pathways, antiapoptotic mechanisms, and modulation of energy metabolism in corpus cavernosum smooth muscle cells (CCSMCs).

Recent investigations have proposed the combined application of MSCs and LI-ESWT as a strategy to optimize the local microenvironment, enhance the survival and functional integration of transplanted cells, and achieve a synergistic therapeutic effect [19]. Preliminary animal studies have demonstrated that such combined therapy can significantly improve the structural and functional integrity of the corpora cavernosa, offering a novel approach to the treatment of diabetic ED [20]. Notably, emerging evidence suggests that combining MSC transplantation with low-intensity extracorporeal shock wave therapy (LI-ESWT) may yield synergistic therapeutic

effects.LI-ESWT has been shown to enhance MSC homing, viability, and paracrine function while independently promoting angiogenesis and tissue regeneration through mechanotransduction pathways [21]. Building upon these preclinical foundations, contemporary research has increasingly focused on combinatorial regenerative strategies integrating mesenchymal stem cells (MSCs) with low-intensity extracorporeal shock wave therapy (LI-ESWT). This dual-modality approach capitalizes on their complementary mechanisms of action: while MSCs provide trophic support and cellular regeneration, LI-ESWT enhances the local tissue microenvironment through mechanobiological stimulation. Current evidence indicates three key synergistic interactions [22], significant improvement in MSC engraftment efficiency, potentiation of angiogenic factor secretion, and preservation of corpus cavernosum structural integrity (75% improvement in elastic fiber density). Particularly in diabetic ED models, this combination has demonstrated superior functional recovery compared to either therapy alone. This combined approach may address current limitations of standalone therapies by simultaneously targeting multiple pathological mechanisms underlying ED. Although preclinical studies demonstrate synergistic effects, critical translational gaps remain, for example, clinical data remain sparse, and the safety, efficacy, and long-term benefits of this approach require further validation.

Therefore, the present study aims to systematically evaluate the efficacy and safety of high-activity hPMSCs in combination with LI-ESWT in patients with diabetic ED through a prospective, randomized, controlled clinical trial. We anticipate that this investigation will not only provide a new therapeutic option for diabetic ED but also furnish robust clinical evidence and theoretical support for a regenerative medicine strategy that integrates stem cell and physical therapies.

Materials and methods

This prospective, randomized, controlled clinical trial aimed to evaluate the efficacy and safety of high-activity placenta-derived mesenchymal stem cells (hPMSCs) combined with low-intensity extracorporeal shock wave therapy (LI-ESWT) in patients with refractory diabetic (type 2 diabetes mellitus) erectile dysfunction (ED). Due to recruitment challenges and ethical considerations, the final sample size was reduced to 11 patients per group. Post-hoc power analysis confirmed retained statistical power (>75%) for primary outcomes, supported by larger-than-anticipated effect sizes. A total of 33 eligible patients were enrolled and randomly assigned in a 1:1:1 ratio into three groups: the hPMSCs group ($n = 11$), the LI-ESWT group ($n = 11$), and the combined therapy group (H + L, $n = 11$). During the study, one patient in the LI-ESWT group withdrew due to unsatisfactory efficacy, and one patient in the combined group was lost to follow-up; all remaining participants completed the study. The study protocol and all procedures were approved by the Institutional Ethics Committee (Approval No. JJ202310-02), and registered for clinical trials (Registration No. ChiCTR2200059271). Written informed consent was obtained from all participants prior to enrollment.

Inclusion and exclusion criteria

Inclusion criteria:

1. Male patients aged 20–60 years with a diagnosis of diabetes for at least 5 years;
2. Overall good health with a stable sexual partner for more than 3 months;
3. A duration of ED of at least 3 months but less than 10 years;
4. Mild to severe ED with an International Index of Erectile Function-Erectile Function (IIEF-EF) score of less than 22;
5. No use of PDE5 inhibitors or other ED treatments within 2 weeks prior to randomization;
6. Voluntary participation in the study with signed informed consent.

Exclusion criteria:

1. Severe endocrine or neurogenic ED;
2. Vascular ED due to penile arterial or cavernosal lesions;
3. Severe psychological disorders, spinal cord injury, anatomical penile abnormalities, or penile hemangiomas;
4. Severe chronic hematological diseases or significant respiratory, gastrointestinal, or central nervous system disorders;
5. History of radical prostatectomy, urethral or penile surgery, or any pelvic, urethral, or penile trauma; patients recovering from cancer in the past year or who have received pelvic radiotherapy;
6. Poor blood pressure control (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg);
7. Poor glycemic control (fasting blood glucose > 7.0 mmol/L);
8. Use of anti-androgens, androgenic drugs, or anticoagulants in the past 4 weeks due to coagulation disorders;
9. Participation in any other clinical trials involving medical devices or drugs within the past 3 months;
10. Any other condition deemed unsuitable for study participation by the investigators.

Interventions

Extraction of mesenchymal stem cells

Human placenta-derived mesenchymal stem cells (hPMSCs) were isolated from placentae obtained from healthy women undergoing full-term cesarean delivery (ethical approval for the use of placenta tissue: Approval No. JJ202310-02; Date: October 30, 2023). The placental tissues were initially rinsed with normal saline and stored in L15 medium containing antibiotics (200 U/mL penicillin and 200 μg/mL streptomycin) under sterile conditions, then transported to the laboratory within 2 h at low temperature. Under aseptic conditions, the placentae were repeatedly washed with phosphate-buffered saline (PBS), minced into small pieces, and digested using a combined enzymatic method. The resultant cell suspension was cultured, and cells were passaged upon reaching 80% confluence until the third passage.

For phenotypic characterization, third-passage hPMSCs were digested with trypsin, centrifuged, and washed. The cell pellet was resuspended in DMEM/F12 medium containing 10% fetal bovine serum, and cells were then stained with 10 μL each of appropriately diluted monoclonal antibodies against CD44, CD90, CD105, CD14, CD34, and HLA-DR, according to the manufacturer's instructions. Flow cytometry was performed to assess cell surface markers. Additionally, third-passage hPMSCs were induced to differentiate into osteogenic, adipogenic, and chondrogenic lineages using respective differentiation media over 21 days.

Cell injection therapy

The hPMSCs were prepared as a cell suspension with a concentration of 1×10^7 cells/mL. Each patient in the hPMSCs group received a single intracavernosal injection. Following disinfection of the penis and application of a penile constriction band at the base, 1 mL of the cell suspension was injected into the corpora cavernosa (0.5 mL per side) using a 1 mL syringe. After injection, local compression was applied for 1 min, and the constriction band was maintained for 30 min before removal.

Low-Intensity Extracorporeal Shock Wave Therapy (LI-ESWT)

LI-ESWT was performed using a shock wave device targeting both sides of the corpora cavernosa and the penile crura. Low-intensity extracorporeal shockwave therapy was administered using the RENOVA® electromagnetic lithotripter (Direx Group, Wiesbaden, Germany). The treatment parameters were set at an energy density of 0.09 mJ/mm² and a pulse frequency of 120 pulses per minute [12]. For each treatment session, five treatment points were designated (covering the distal, mid, and proximal regions of the penis, as well as the left and right penile crura), with 1,000 shocks delivered at each point, amounting to a total of 5,000 shocks per session. The LI-ESWT protocol was applied independently in the LI-ESWT group, while the combined therapy group (H + L) received both LI-ESWT and hPMSCs injection.

Combined intervention therapy

Participants in the combined intervention group underwent a sequential therapeutic protocol: (1) a intracavernous injection of placental mesenchymal stem cells (PMSCs) was administered at baseline, followed by (2) low-intensity extracorporeal shockwave therapy (LI-ESWT) initiated 24 h post-injection. The LI-ESWT regimen consisted of four weekly sessions.

Informed consent process

The process included the following steps: Written Consent Document: Participants received a standardized, ethics committee-approved consent form written in lay language. The document outlined: Study Objectives: Explanation of the trial's purpose to evaluate the safety and efficacy of combined hPMSCs and LI-ESWT therapy. Procedures: Detailed descriptions of interventions (e.g., stem cell injection protocols, LI-ESWT sessions), follow-up assessments, and potential risks (e.g., mild pain, bruising). Rights of Participants: Assurance of voluntary participation, the right to withdraw at any time without penalty, and continued access to standard care. Confidentiality: Measures to anonymize data and protect personal health information. Verbal Explanation: A physician or study coordinator verbally reviewed the consent form with each participant, ensuring comprehension of key elements. Participants were encouraged to ask questions, which were addressed immediately. Assurance of Understanding: For participants with limited literacy or language barriers, a family member or independent witness (unaffiliated with the study team) was present during the consent process. Ongoing Consent: Participants were reconsented if significant protocol modifications occurred during the trial.

Outcome parameters

The primary efficacy endpoint was the median change in IIEF-EF scores from baseline. Secondary endpoints included the Erection Hardness Score (EHS), the success rates of sexual encounters as recorded in the Sexual Encounter Profile (SEP-2 for successful penetration and SEP-3 for successful intercourse), and NPT-Rigiscan parameters (total erection time, sufficient erection time, and penile hardness measurements). NPT-Rigiscan measurements were interpreted using consensus thresholds from the International Society for Sexual Medicine: (1) ≥ 3 erectile events/night; (2)Tip rigidity ≥ 60% sustained for ≥ 10 min; (3)Base rigidity ≥ 60% sustained for ≥ 10 min. Comprehensive evaluations were conducted at baseline, 1 month, 3 months, and 6 months post-treatment, with

adverse events recorded at each follow-up visit. To minimize confounding, all patients discontinued any other ED medications during the study period and for a 2-week washout period prior to intervention.

Statistical analysis

A generalized estimating equation (GEE) model was employed to analyze the primary outcome measures, incorporating data from baseline, 1 month, 3 months, and 6 months. The model included treatment group, follow-up time, and the interaction between treatment group and follow-up time as independent variables, with baseline values of continuous variables used as covariates to adjust for initial differences. Continuous variables were expressed as mean ± standard deviation after testing for normality; if data were normally distributed, independent-sample t-tests were used, otherwise the Wilcoxon rank-sum test was applied. Categorical variables were summarized as frequencies and percentages, and group comparisons were performed using the chi-square test or Fisher's exact test. Continuous variables are reported as medians (interquartile range) due to non-normal distributions confirmed by Shapiro-Wilk testing. Parametric assumptions were violated; thus, non-parametric tests were utilized for hypothesis testing. All statistical tests were two-tailed, and a p-value of ≤ 0.05 was considered statistically significant.

Result

A total of 55 participants were initially recruited for the study. Following rigorous screening, 22 subjects were excluded because they did not meet the preset criteria: 15 voluntarily withdrew, 3 exhibited poor blood pressure control, 2 had inadequate glycemic management, and 2 presented with comorbidities incompatible with the study protocol. Ultimately, 33 eligible participants were randomly allocated using a computer-generated randomization system into three intervention groups ($n = 11$ per group): the hPMSCs group, the LI-ESWT group, and the combined therapy group (H + L). During the study, two participants discontinued treatment—one in the hPMSCs group due to unsatisfactory efficacy and one in the H + L group for personal reasons (unforeseen relocation necessitating interstate migration) (Fig. 1). As shown in Table 1, the demographic and baseline clinical characteristics were comparable among the three groups. Notably, there were no statistically significant differences at baseline in the International Index of Erectile Function-Erectile Function (IIEF-EF) scores, Erection Hardness Score (EHS), or the nocturnal penile tumescence (NPT-Rigiscan) parameters (Table 2), thereby establishing reliable baseline comparability for subsequent outcome evaluations.

The baseline IIEF-EF scores were similar across the hPMSCs, LI-ESWT, and H + L groups ($p > 0.05$). Longitudinal analysis demonstrated an improvement in IIEF-EF scores over time in all treatment arms. Importantly, the H + L group consistently exhibited the most pronounced therapeutic effect at all follow-up time points

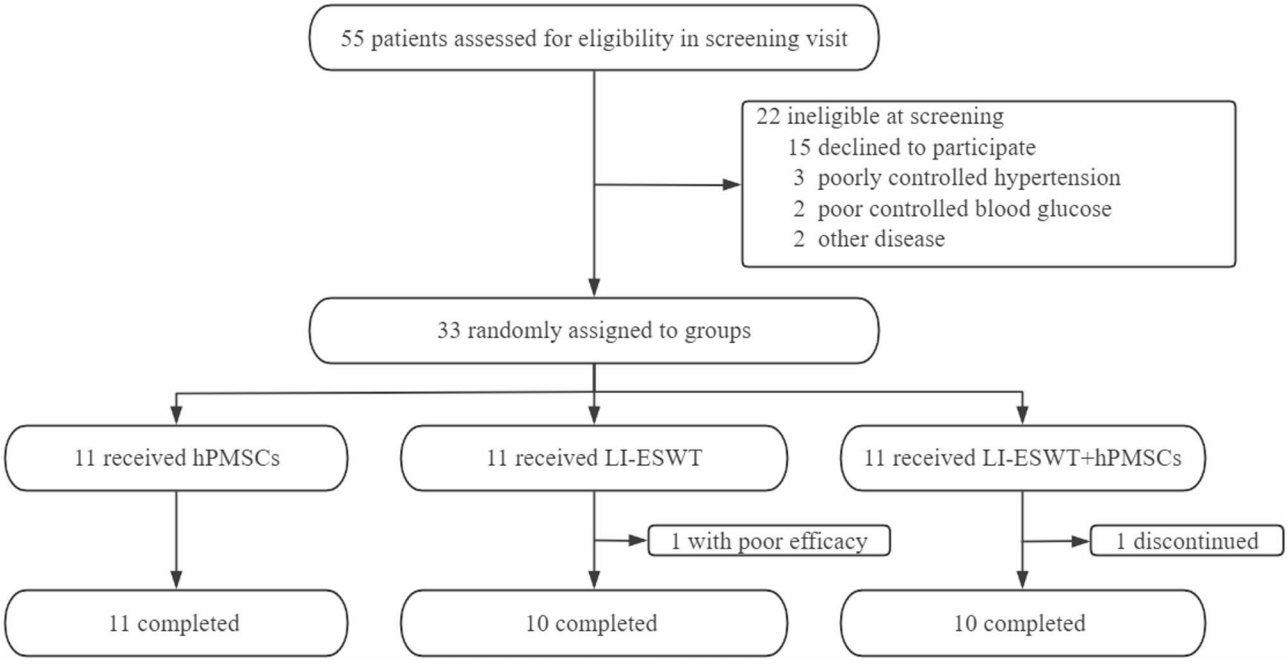

Fig. 1 Trial profile

Table 1 Baseline characteristics of study participants

	hPMSCs (*n* = 11)	LI-ESWT (*n* = 10)	H + L (*n* = 11)	*P*
Age M (Q_1, Q_3)	53.00 (49.50,58.00)	54.00 (51.00,59.75)	59.00 (54.50,60.00)	0.139
BMI M (Q_1, Q_3)	25.60 (23.85,28.80)	26.45 (23.05,28.82)	27.80 (24.35,29.00)	0.787
ED time M (Q_1, Q_3)	3.50 (3.10,4.45)	4.15 (3.40,4.65)	5.10 (3.80,5.90)	0.145
IIEF-EF M (Q_1, Q_3)	12.00 (10.50,15.00)	11.00 (10.00,11.75)	13.00 (11.50,14.00)	0.212
Patients with positive SEP-2(%)	2 (18.18)	3 (30.00)	2 (18.18)	0.757
Patients with positive SEP-3 (%)	2 (18.18)	1 (10.00)	1 (9.09)	1.000
Patients with EHS > 2	2 (18.18)	3 (30.00)	2 (18.18)	0.757

Data are presented as median (interquartile range) or n (%)

Table 2 Baseline characteristics of Rigiscan

Rigiscan	hPMSCs (*n* = 11)	LI-ESWT (*n* = 10)	H + L (*n* = 11)	*P*
Total Erection Time M (Q_1, Q_3)	0.00 (0.00,1.50)	0.00 (0.00,1.50)	0.00 (0.00,2.50)	0.698
Average Rigidity at Coronary Sulcus M (Q_1, Q_3)	31.00 (23.50,33.50)	29.50 (26.25,33.75)	29.00 (23.00,36.50)	0.931
Average Rigidity at Base M (Q_1, Q_3)	28.00 (21.00,30.50)	27.00 (22.00,32.00)	26.00 (21.50,32.50)	0.727
Maximum Rigidity at Coronary Sulcus M (Q_1, Q_3)	51.00 (44.50,57.50)	48.50 (44.75,51.00)	52.00 (50.50,56.00)	0.249
Maximum Rigidity at Base M (Q_1, Q_3)	41.00 (36.50,44.50)	40.00 (34.00,44.25)	41.00 (35.00,43.50)	0.895
Swelling Increase-at CoronarySulcus M (Q_1, Q_3)	0.50 (0.25,1.00)	0.50 (0.00,1.00)	1.00 (0.00,1.00)	0.661
Swelling Increase at Base M (Q_1, Q_3)	0.00 (0.00,1.00)	1.00 (0.00,1.00)	1.00 (0.00,1.00)	0.530

Data are presented as median (interquartile range) or n (%)

(1, 3, and 6 months), with significantly higher IIEF-EF scores compared to the single-therapy groups ($p < 0.05$; Fig. 2). Specifically, at the 1-month follow-up, the H + L group's score significantly increased from a baseline of 13.09 ± 0.69 to 14.11 ± 0.61, outperforming both the hPMSCs group (11.22 ± 0.91) and the LI-ESWT group (12.00 ± 0.25) ($p < 0.05$). At 3 months, the H + L score further increased to 16.90 ± 0.43, maintaining its significant advantage over the hPMSCs (13.11 ± 0.60) and LI-ESWT groups (13.75 ± 0.86) ($p < 0.05$). At 6 months, the combined therapy group achieved a mean IIEF-EF score of 19.8 ± 0.31, which remained significantly higher than the hPMSCs group (17.50 ± 0.53) and the LI-ESWT group (16.67 ± 1.39) ($p < 0.05$). These findings indicate that over the 6-month observation period, the combined H + L therapy produced a sustained and superior therapeutic effect compared to either monotherapy, suggesting a potential for enhanced and lasting benefits in erectile function recovery.

Regarding EHS, at baseline and the 1-month follow-up, the proportion of patients with EHS > 2 was similar among the groups (hPMSCs: 18.18%, LI-ESWT: 30%, H + L: 18.18%; $p = 0.757$). By 3 months, although the proportion of patients with EHS > 2 increased in all groups, the intergroup differences remained statistically insignificant ($p = 0.894$). Notably, at the 6-month follow-up, the H + L group exhibited a significantly higher proportion of patients with EHS > 2 (70%) compared to the hPMSCs (45.45%) and LI-ESWT (40%) groups ($p = 0.045$). In contrast, at the 1-month and 3-month assessments, the success rates recorded as SEP-3 (successful intercourse) did not show significant improvement or intergroup differences ($p > 0.05$). At 6 months, SEP-3 positivity reached 18.18% in the H + L group, 30% in the LI-ESWT group, and remained at 18.18% in the hPMSCs group, with the differences not achieving statistical significance ($p = 0.789$) (Table 3). These results suggest that while the combined H + L treatment appears to be more effective in enhancing erection hardness (EHS > 2), its

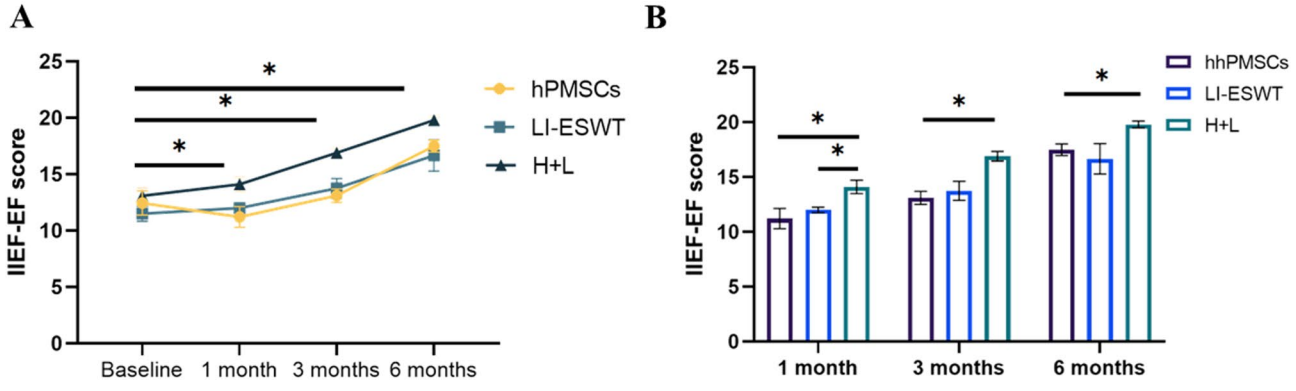

Fig. 2 (**A**) Trend of IIEF-EF Scores Over Time; (**B**) Comparison of IIEF-EF Scores Among Different Groups at Each Time Point

Table 3 Comparison of patients between LI-ESWT hPMSCs and H + Lwith EHS SEP-2 and SEP-3

	hPMSCs	LI-ESWT	H + L	*P*-value
Patients with EHS > 2				
Baseline	2(18.18)	3(30)	2(18.18)	0.757
1 month	2(18.18)	3(30)	2(18.18)	0.757
3 months	4(36.30)	4(40)	3(27.27)	0.894
6 months	5(45.45)	4(40)	7(70)	0.045*
Patients with positive SEP-2 (%)				
Baseline	2(18.18)	3(30)	2(18.18)	0.757
1 month	3(27.27)	4(40)	3(27.27)	0.869
3 months	3(27.27)	4(40)	4(36.36)	0.866
6 months	3(27.27)	4(40)	4(36.36)	0.866
Patients with positive SEP-3 (%)				
Baseline	2(18.18)	1(10)	1(9.09)	1.000
1 month	2(18.18)	1(10)	1(9.09)	1.000
3 months	2(18.18)	2(20)	1(9.09)	0.898
6 months	2(18.18)	3(30)	2(18.18)	0.789

impact on overall sexual performance—reflected by both SEP-2 (penetration success) and SEP-3 (successful intercourse) rates—remains limited and warrants further investigation.

All groups experienced a significant increase in total erection time from baseline to the 6-month follow-up ($p < 0.001$). At 6 months, the median total erection time was 18.20 min (IQR: 13.35–20.55) in the hPMSCs group, 11.00 min (IQR: 11.00–12.00) in the LI-ESWT group, and 22.20 min (IQR: 15.20–30.25) in the H + L group, with statistically significant differences among groups (χ^2 = 13.68, $p = 0.001$). Post-hoc pairwise comparisons revealed that the H + L group had a significantly longer total erection time than both the LI-ESWT (Z = 7.0, $p < 0.01$) and the hPMSCs groups (Z = 92.0, $p < 0.01$). Similarly, effective erection time, which was 0.00 min (IQR: 0.00–0.00) at baseline across all groups, improved significantly by 6 months to 11.40 min (IQR: 10.75–12.00) in the hPMSCs group, 10.70 min (IQR: 10.33–11.28) in the LI-ESWT group, and 11.90 min (IQR: 11.55–12.35) in the H + L group (χ^2 = 11.14, $p = 0.004$). Post-hoc analysis demonstrated that the effective erection time in the H + L group was significantly longer than in the LI-ESWT group (Z = 7.5, $p < 0.01$). Improvements in penile hardness at the coronal sulcus and base were observed in all groups; however, the intergroup differences did not reach statistical significance. Additionally, changes in swelling at the coronal sulcus and base were similar across the groups (χ^2 = 0.23, $p = 0.893$) (Table 4). In summary, the combined hPMSCs and LI-ESWT therapy (H + L group) demonstrated a significantly greater improvement in both total and effective erection times compared to either monotherapy. Although improvements in penile hardness and swelling were observed, these parameters did not differ significantly between groups.

Table 4 Comparison of patients between LI-ESWT hPMSCs and H + L with Rigiscan

Group	Index	Baseline	6 - month Follow - up	χ^2	*P*
hPMSCs*	Total erection time	0.00 (0.00, 1.50)	18.20 (13.35, 20.55)	13.68	0.001
LI-ESWT*[a]		0.00 (0.00, 1.50)	11.00 (11.00, 12.00)		
H + L[a]		0.00 (0.00, 2.50)	22.20 (15.20, 30.25)		
hPMSCs	Sufficient erection time	0.00 (0.00, 0.00)	11.40 (10.75, 12.00)	11.14	0.004
LI-ESWT*		0.00 (0.00, 0.00)	10.70 (10.33, 11.28)		
H + L*		0.00 (0.00, 0.00)	11.90 (11.55, 12.35)		
hPMSCs	Average hardness at coronal sulcus	31.00 (23.50, 33.50)	47.00 (46.50, 48.50)	5.80	0.055
LI-ESWT		29.50 (26.25, 33.75)	47.50 (44.25, 48.00)		
H + L		29.00 (23.00, 36.50)	49.00 (48.00, 50.50)		
hPMSCs	Average hardness at base	28.00 (21.00, 30.50)	46.00 (44.50, 47.00)	5.13	0.077
LI-ESWT		27.00 (22.00, 32.00)	44.00 (42.00, 45.75)		
H + L		26.00 (21.50, 32.50)	47.00 (45.00, 48.00)		
hPMSCs	Increase in swelling at coronal sulcus	0.50 (0.25, 1.00)	1.70 (1.65, 1.80)	0.23	0.893
LI-ESWT		0.50 (0.00, 1.00)	1.75 (1.70, 1.87)		
H + L		1.00 (0.00, 1.00)	1.70 (1.70, 1.80)		
hPMSCs	Increase in swelling at base	0.00 (0.00, 1.00)	1.70 (1.65, 1.80)	0.23	0.893
LI-ESWT		1.00 (0.00, 1.00)	1.75 (1.70, 1.87)		
H + L		1.00 (0.00, 1.00)	1.70 (1.70, 1.80)		

hPMSCs group (high-activity placenta-derived mesenchymal stem cells group), LI-ESWT group (low-intensity extracorporeal shock wave therapy group), and H + L group (combined treatment group); *: pairwise comparisons post-treatment, $p < 0.05$; a: pairwise comparisons post-treatment, $p < 0.05$

Safety assessments throughout the study evaluated potential adverse events, including pain, hematoma, hematuria, and bruising. No severe adverse events were reported in any treatment group. Notably, some patients in the hPMSCs and H + L groups experienced mild, localized pain; according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, these were classified as Grade 1 events (mild) and were self-limited, resolving within one week without the need for medical intervention. Overall, both the hPMSCs monotherapy and the combined LI-ESWT treatment regimen demonstrated a favorable safety profile in the management of erectile dysfunction.

Discussion

Diabetes mellitus induces progressive deterioration of vascular endothelial function [23], accompanied by significant reduction in cyclic guanosine monophosphate (cGMP) levels, which consequently attenuates the therapeutic efficacy of phosphodiesterase type 5 inhibitors (PDE5i) [24]. Emerging evidence demonstrates that transplantation of mesenchymal stem cells (MSCs) from various sources can markedly improve erectile function and ameliorate histopathological alterations in the corpus cavernosum of diabetic ED rat models [25, 26]. However, the diabetes-specific pathological microenvironment, characterized by persistent hyperglycemia and exacerbated oxidative stress within the cavernous tissue [27], substantially compromises the survival and functionality of transplanted stem cells, thereby limiting their therapeutic potential. While autologous dermal sheath cup cells (ADSCs) have been widely utilized in erectile dysfunction (ED) management due to their accessibility and potential for autologous transplantation [28, 29], human placental mesenchymal stem cells (hPMSCs) demonstrate superior capacity in secreting pro-regenerative cytokines critical for counteracting diabetes-induced microvascular damage and neuronal degeneration [30]. Notably, hPMSCs exhibit enhanced immunomodulatory properties through dual mechanisms: (1) suppression of pro-inflammatory mediators (TNF-α, IL-6) and (2) activation of regulatory T cell populations, biological effects particularly beneficial for mitigating chronic inflammation-associated corpus cavernosum fibrosis and endothelial dysfunction [31]. From a practical perspective, placental tissue represents an ethically non-controversial and abundant stem cell source that can be non-invasively procured during routine cesarean deliveries. While ADSCs remain a cornerstone of ED research, hPMSCs offer distinct advantages in trophic support, diabetic microenvironment adaptability, and clinical scalability.

Previous studies have established the therapeutic promise of low-intensity extracorporeal shock wave therapy (LI-ESWT) in diabetic models. Hayashi et al. reported that LI-ESWT significantly upregulates the expression of pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), in diabetic mice [32]. Further investigations by Li et al. revealed that LI-ESWT promotes the recruitment of endogenous progenitor cells and activates Schwann cells in a rat model of pelvic nerve injury, thereby synergistically enhancing angiogenesis, tissue repair, and neural regeneration [33]. Given that both MSCs and LI-ESWT exert their regenerative effects predominantly through paracrine secretion of growth factors, we hypothesize that their combined application may yield synergistic therapeutic outcomes.

This prospective clinical investigation systematically evaluated the therapeutic efficacy and safety profile of high-activity placental mesenchymal stem cells (hPMSCs) combined with low-intensity extracorporeal shock wave therapy (LI-ESWT) in patients with refractory diabetic erectile dysfunction (ED).Our findings indicate that the combined treatment regimen (H + L group) produced significantly superior improvements in erectile function compared to either hPMSCs or LI-ESWT monotherapy, as evidenced by enhanced International Index of Erectile Function-Erectile Function (IIEF-EF) scores, increased total and effective erection times, and improved Erection Hardness Scores (EHS). The H + L group exhibited a sustained and progressive improvement in IIEF-EF scores over the 6-month follow-up period. At each time point (1, 3, and 6 months), the combined therapy group achieved significantly higher scores than the individual treatment groups. These data suggest a potential synergistic effect when combining cellular therapy with physical stimulation, likely attributable to the enhanced microenvironment that promotes cell survival and functionality [11].

The mechanisms underlying the observed synergistic effect may involve multiple pathways. LI-ESWT is known to induce mechanical stress [34] that stimulates the release of endogenous cytokines, growth factors, and nitric oxide, thereby promoting angiogenesis and nerve regeneration [35]. Meanwhile, hPMSCs exert their therapeutic effects predominantly through paracrine signaling, releasing a variety of bioactive molecules such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) [36], which facilitate tissue repair and regeneration [37]. The concurrent use of LI-ESWT may improve the local milieu within the corpora cavernosa, enhancing the engraftment and paracrine activity of transplanted hPMSCs [38, 39], thus leading to more pronounced improvements in erectile function.

Notably, while significant improvements were observed in total and effective erection times and EHS—particularly at the 6-month assessment—the improvements in other parameters such as penile hardness at the coronal sulcus and base, as well as sexual encounter profile indices (SEP-2 and SEP-3), were less pronounced. This discrepancy may arise from the inherent complexity of SEP as a measure of real-world sexual performance, which is influenced by multifactorial determinants. In diabetic ED, psychological comorbidities—including anxiety, depression, and performance-related stress—often persist despite physiological improvements, thereby inhibiting successful intercourse. Furthermore, patients with chronic ED may require prolonged adaptation periods to rebuild confidence and integrate restored erectile function into sexual activity, potentially delaying observable SEP improvements beyond the 6-month follow-up window. Additionally, SEP outcomes are context-dependent,

modulated by transient factors such as fatigue and stress, which are not readily quantified in standardized clinical assessments. The lack of statistically significant differences in these measures suggests that while the combined treatment effectively enhances certain aspects of erectile function, its impact on overall sexual performance (including penetration and intercourse completion) may be limited. These findings underscore the need for further research to elucidate the mechanisms and to optimize the treatment protocol for a more comprehensive restoration of sexual function.

The safety profile of the combined treatment was favorable. No severe adverse events were recorded throughout the study period, and only minor, self-limiting adverse events (e.g., mild local pain) were observed in the hPMSCs and H + L groups. This supports the clinical feasibility of employing a combined regenerative approach in the management of diabetic ED.

Notably, this study has several limitations. The modest sample size and short follow-up period restrict the generalizability of our findings. While statistically significant improvements were observed, larger multicenter studies with extended follow-up are warranted to confirm long-term efficacy, safety, and broader applicability. Furthermore, the exclusion of men with same-sex partners or non-stable relationships introduces selection bias, narrowing the external validity of results and perpetuating systemic underrepresentation of sexual orientation in clinical research. This design flaw highlights the urgent need for inclusive methodologies in future trials to address the heterogeneity of sexual health needs across diverse populations. While our combined therapy demonstrated significant improvements in erectile physiology, the limited success in SEP-3 outcomes highlights the need for integrative approaches addressing psychological and relational factors. Future studies should incorporate psychometric evaluations and partner-inclusive assessments to optimize therapeutic outcomes and patient satisfaction. Our cohort primarily comprised older adults with longstanding Type 2 diabetes, limiting generalizability to younger populations with juvenile-onset disease. The single patient aged 20–30 years (diabetes onset at 15 years) underscores the need for dedicated studies in this high-risk subgroup, where early vascular damage may necessitate aggressive regenerative strategies. Additionally, the mechanisms behind the synergistic effect of LI-ESWT and hPMSCs require further investigation through mechanistic studies and larger clinical trials.

Conclusion

In conclusion, our study provides preliminary evidence that the combination of high-activity hPMSCs and LI-ESWT is a safe and more effective therapeutic strategy for improving erectile function in patients with diabetic ED compared to either treatment alone. The synergistic enhancement observed in erection duration and hardness suggests that this combined modality may offer a promising avenue for the development of long-term regenerative treatments for ED. Future large-scale, multicenter studies with extended follow-up periods are warranted to validate these findings and to further explore the underlying biological mechanisms.

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Author contributions
JYH, TX, HHZ and YZ performed the data analysis. JYH and ZB drafted the manuscript. ZYF and YZ revised the manuscript. ZB and YZ conceived the study and supervised the project. All authors read and approved the final version of the manuscript.

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Data availability
The datasets generated and analyzed during the current study are not publicly available due to privacy but are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Tangdu Hospital of Air Force Military Medical University approved the study protocol entitled "Clinical Study of Placenta-Derived Mesenchymal Stem Cells Combined with Microenergy for Treatment of Erectile Dysfunction in Diabetes Mellitus" under approval number JJ202310-02 on October 30, 2023. The ethical approval encompassed the use of placenta tissue, and no additional approval was necessary. All participants provided written informed consent and all study procedures, including the use of human placenta tissue for mesenchymal stem cell isolation, were conducted in accordance with the Declaration of Helsinki. All participants received both written and verbal explanations of the study's risks, benefits, and alternatives, with measures to ensure comprehension across diverse literacy levels. Trial registration: ChiCRT2200059271. Registered April 27th 2022, https://www.chictr.org.cn.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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