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Recent advances in stem cell therapy for erectile dysfunction: a narrative review

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Abstract

Introduction: While phosphodiesterase type 5 inhibitors (PDE5is) and others are used to treat Erectile dysfunction (ED), many patients are either unresponsive or resistant to it. Stem cell therapy (SCT) is a promising alternative approach. Numerous preclinical trials have demonstrated improved erectile function in animal models using SCT, although the number of clinical trials investigating SCT for men with ED is limited. Nonetheless, findings from human clinical trials suggest that SCT may be a useful treatment option.

Areas covered: Biomedical literature, including PubMed, ClinicalTrials.gov, and European Union Clinical Trails Registry, were analyzed to summarize and synthesize information on stem cell therapy for ED in this narrative review. The achievements in preclinical and clinical evaluations are presented and critically analyzed.

Expert opinion: SCT has demonstrated some benefits in improving erectile function, while further studies are urgently needed. Such studies would provide valuable insights into the optimal use of stem cell therapy and its potential as a therapeutic option for ED. Taking advantage of different mechanisms of action involved in various regenerative therapies, combination therapies such as SCT and low-energy shock waves or platelet-rich plasma may provide a more effective therapy and warrant further research.

Keywords

Erectile dysfunction; Stem cell therapy; Clinical trial; Side effects

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Declaration of interest

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1. Introduction

Erectile dysfunction (ED) is a prevalent male sexual dysfunction characterized by the inability to achieve and maintain an erection sufficient for satisfactory sexual performance [1]. ED can have a significantly negative impact on a patient's quality of life and can strain the patient's relationship with their partner [2,3]. Studies estimate that ED affects 52% of men between the ages of 40 and 70 [4]. Diabetes mellitus is a significant risk factor for ED, with diabetic men having a 2 to 3 times higher incidence rate than non-diabetics[5]. Other well-known risk factors include old age, obesity, smoking, hypertension, coronary artery disease, pelvic and prostate surgery, testosterone and hypogonadism, and other conditions [6–8] [9]. The causes of ED are classified as psychogenic or organic, with organic causes including neurogenic, vasculogenic, iatrogenic, and endocrine disorders [10]. Current medical treatments for non-endocrine organic ED include oral phosphodiesterase type 5 inhibitors (PDE5i), intracavernosal injections (ICI), vacuum erection devices (VEDs), intraurethral (IU) alprostadil suppositories, and penile implants [11]. However, these treatments only relieve and ameliorate symptoms without addressing the underlying pathology of the penile tissue.

Restorative therapies for ED include stem cell therapy (SCT), platelet-rich plasma therapy (PRP), low-intensity extracorporeal shockwave therapy (Li-ESWT), low-intensity pulsed ultrasound therapy (LIPUS) [12,13], nanomedicine, and gene therapy [14]. SCT has shown promise in both animal models and humans [15].

Two significant breakthroughs in stem cell research are multipotent embryonic stem cells (ES cells) and induced stem cells (iPS cells), both of which have similar trans-differentiation potentials [16] [17]. However, the clinical applications of ES and iPS cells are currently limited due to biosafety concerns and the risk of uncontrolled differentiation to tumors and undesired tissues [18,19]. Different types of mesenchymal stem cells (MSCs) have pro-regenerative and immune-modulatory paracrine effects, making them suitable for therapeutic use [19] [20]. These findings have shifted the focus of stem cell therapy from tissue engineering to therapies based on the paracrine effects of stem cells. The activity of stem cells is less dependent on "stemness" and more on the indirect paracrine effects mediated by the secretome of locally injected stem cells [21,22] [23].

SCT has been studied for ED since the 2000s, and various animal models have shown that stem cells can improve erectile function [15]. However, few human clinical trials have been reported, and the data are far from conclusive [15]. The aim of this article is to summarize the clinical trials of SCT for the treatment of men with ED.

2. Literature search methodology

The databases of PubMed, ClinicalTrials.gov, and European Union Clinical Trails Registry (www.clinicaltrailsregister.eu) website were searched using the keyword combinations "stem cell therapy," "erectile dysfunction," "clinical trials," and "side effect." We also retrieved reports from the United States National Institute of Health database and European Union Clinical Trials Registry by using the search terms "stem cell" and "erectile dysfunction".

The inclusion criteria were full-text articles written in English and published from 2000 to 2023. Articles were initially selected based on their titles and abstracts. The full text of the papers was reviewed, and those that did not fit the purpose of this review or did not provide sufficient data for a complete assessment were excluded. The quality of the research articles and other publications included in the review was assessed, including the study design, methodology, and potential biases. The results were comprehensively analyzed.

3. Preclinical and clinical studies

Stem cell therapy for ED is a promising approach that involves the use of stem cells to regenerate damaged or diseased tissues in the penis, thereby restoring erectile function. The mechanism of action of stem cell therapy for ED is thought to involve several different pathways, including neovascularization, anti-inflammatory effects, tissue regeneration, and neuroprotection. Most of the basic research findings suggest that the paracrine effects of the injected stem cells are the main drivers of the beneficial effects. In one animal study, the authors reported that the implanted stem cells, both bone marrow-derived and adipose-derived, did not turn into the host cells and migrated to other organs such as the lung and bone marrow [24]. Therefore, more research is needed to fully understand the mechanism of action and optimize the therapeutic potential of this approach [25] [26].

Preclinical and clinical research on stem cell therapy for ED has been ongoing since 2004, when Bochinski et al. injected embryonic stem cells into the corpora cavernosa of rats with ED after cavernous injury [27]. Following this initial study, subsequent preclinical studies examined the effects of stem cell treatment on ED resulting from various causes such as aging, diabetes, hyperlipidemia, radiation injury, and others [28–38]. The first clinical trial of stem cell therapy for ED was published in 2010, in which seven ED patients with diabetes mellitus received human umbilical cord blood stem cells (hUCBSCs). The results of this study showed modest positive effects on erectile function and blood sugar levels [39].

The therapeutic effect of SCT for ED is attributed to paracrine effects that enhance the function of smooth muscle and nerves in the corpus cavernosum [40–42]. This theory is derived from the observation that adipose-derived regenerative cell lysate exhibited similar beneficial effects as intact cells in a rat model of ED caused by cavernous nerve crush injury [43]. Preclinical studies have demonstrated that injected stem cells exert cytoprotective, anti-fibrotic, anti-inflammatory, pro-regenerative, immune-modulating, and antiapoptotic effects [44]. Other mechanisms include neurotrophic effects on the cavernous nerves and activation of host progenitor cells [45]. Moreover, some degree of engraftment and cellular differentiation may also contribute to the favorable outcomes [46]. Overall, stem cell therapy for ED is a promising approach that has shown positive results in preclinical and clinical studies. However, more research is needed to fully understand the mechanism of action and optimize the therapy for maximum efficacy.

4. Type of stem cells used in clinical trials for ED

Stem cells are either undifferentiated or partially differentiated cells that have the potential to differentiate into a range of cell types and possess self-renewal ability [47,48]. The two

primary sources of stem cells are embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs are derived from the inner cell mass of preimplantation embryos [49]. However, the application of ESCs is limited due to biological and ethical concerns [50]. In contrast, there are fewer ethical concerns associated with the use of ASCs, and their therapeutic potential in regenerative medicine has been well-documented [51]. The types of stem cells used in ED treatment include autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) and autologous adipose-derived stem cells (ADSCs). Due to their low immunogenicity, several perinatal tissue-derived cells or bioactive factors, such as hUCBSCs, Wharton's Jelly-derived mesenchymal stem cells, placental matrix-derived mesenchymal stem cells (PL-MSCs) [28,46,52–55], and acellular solutions from umbilical cord tissue, have also been used as an allogeneic source for ED treatment.

5. Results of clinical trials

Existing clinical trials suggest that stem cell therapy for ED has the potential to improve erectile function and may be a safe and effective treatment option. Larger and more rigorous clinical trials are needed to confirm these findings and to determine the optimal dosage, timing, and delivery methods of stem cell therapy for ED. Table 1 summarizes the characteristics and key outcomes of published clinical trials investigating SCT for ED.

5.1. Allogeneic SC or bioactive factors used in ED therapy

5.1.1 Clinical trials with human umbilical cord blood stem cells—HUCBSCs are a rich source of cytokines and growth factors with high regenerative potential. Wu et al. [56]reported that the supernatant of cultured hUCBSCs contains several bioactive factors, including hepatocyte growth factor (HGF), angiopoietin-1 (Ang-1), vascular endothelial growth factor (VEGF), vascular cell adhesion molecule-1 (VCAM-1), insulin-like growth factor I (IGF-I), prostaglandin E2 (PGE2), and transforming growth factor beta 1 (TGF-β1). Among the tested perinatal tissue stem cells, hUCBSCs secreted the highest amount of IGF-1.

The first clinical trial of stem cell therapy for ED was reported in 2010 [39]. In this study, seven ED patients with type 2 diabetes were treated with hUCBSCs injections into the corpora cavernosa of patients aged 57 to 87 years old. International Index of Erectile Function-5 (IIEF-5) scores, sexual encounter profile (SEP), global assessment questionnaire (GAQ), erection diary, and blood glucose levels were used to evaluate the outcomes. The results showed that most participants regained morning erections, and there was a reduction in blood glucose and glycosylated hemoglobin levels, indicating positive effects on both ED and diabetes mellitus. However, none of the men were able to achieve penetrative sex without a PDE5 inhibitor. Because only 7 patients were recruited for this pilot trial and none of the patients regained normal erectile function, the clinical impact of this study is minimal.

5.1.2. Clinical trials with allogeneic Wharton's Jelly-derived mesenchymal stem cells—Wharton's jelly is a gelatinous substance found within the umbilical cord, containing a variety of growth factors, cytokines, pathway signaling molecules, and stem cells with regenerative properties. These stem cells are not tumorigenic, and their immune privilege ensures histocompatibility. In a phase 1/2 clinical trial (NCT02945449), Demour et

al. (2021) reported the safety and efficacy of two consecutive intracavernosal injections (IC) of allogeneic Wharton's Jelly-derived mesenchymal stem cells (WJ-MSCs) for the treatment of 32 diabetic patients with refractory ED[57]. The study enrolled men with type 1 or 2 diabetes aged between 25–75 years who had a poor response to previous medical therapies, such as PDE-5 inhibitors and prostaglandin E1. Efficacy was assessed using the IIEF-5 and EHS at 1, 3, 6, and 12 months, while penile color duplex ultrasound (CDU) was performed 3 months after the second IC injection. The IIEF-5 scores significantly improved at all follow-up time points, with maximum improvement observed after 6 months. Additionally, the EHS score, mean basal PSV, and 20-min PSV after IC injection were higher than the baseline data. The results of the 12-month follow-up of color duplex doppler ultrasound (CDDU) also demonstrated improvements in penile hemodynamics. However, the positive effects declined between the 6-month and 12-month follow-up periods, suggesting that the treatment may need to be repeated. Because allogeneic Wharton's Jelly-derived mesenchymal stem cells can be used as an allogeneic source of SCT, this approach may have practical clinical utility.

5.1.3. Clinical trials with placental matrix-derived mesenchymal stem cells (PM-MSCs)—Compared to other tissue sources, fresh human placenta is a readily available source for harvesting large numbers of human stem cells for allogenic use. Cells derived from the neonatal tissues of the placenta (hPSCs) can undergo extended expansion with a low risk of senescence. The low expression of HLA class I and II of these cells reduces the risk of rejection in allogeneic applications. The main advantage of hPSC-based therapies seems to lie in the secretion of a wide range of pro-regenerative and anti-inflammatory factors, making hPSCs a highly competent cell for therapy in humans [23].

In a study with the clinical trial identifier NCT02398370 [58], eight patients with organic ED who had failed oral ED medications were treated with placental matrix-derived mesenchymal stem cells (PM-MSCs). A solution comprising 1 mL of PM-MSCs diluted in 2 mL of isotonic saline was prepared, and 1.5 mL was injected into the corpora cavernosa. The number of PM-MSCs was not quantified, and no immunosuppressive therapy was used, nor was any additional PM-MSC injection given. The patients were followed for 6 weeks, 3 months, and 6 months. Although no statistically significant changes were observed in measured end-diastolic velocity, stretched penile length, penile width, and International Index of Erectile Function scores, a significant improvement in mean peak systolic velocity suggestive of improved blood flow was noted at 3 and 6 months. None of the patients were able to achieve satisfactory erections without the aid of oral ED medications or injectables. The only reported side effect was irritation at the injection sites in three men. The small sample size (n=8) is a major limitation of this study. Fresh neonatal tissue from the human placenta is an excellent source for harvesting large numbers of human stem cells for allogeneic use and could be clinically useful. Nevertheless, further randomized, double-blinded controlled trials with larger populations are needed to evaluate the long-term efficacy, safety, need for repeated treatment, and adverse outcomes [58].

5.1.4. Clinical trials with umbilical tissue-derive bioactive molecules—In addition to clinical research with stem cells for ED, a prospective study involving a stem cell-derived product was conducted. Schwarz et al. (2021) evaluated the efficacy

and life quality of patients who received treatment with stem cell-derived bioactive molecules (NCT04684602) [59]. The stem cell-derived product used in this study was a highly concentrated acellular solution sourced from umbilical cord tissue without blood cells or blood products. Twenty self-reported ED men were treated with 2mL of aliquot PrimeProTM (Thoms Advanced Medical, Los Angeles, CA), while six more ED patients received 2ml of saline as a control group. IIEF-5 scores, blood pressure, heart rate, six-minute walk test (6MWT), and the short-form 36 quality of life questionnaire (SF-36) results were recorded at baseline and followed up for six months. The IIEF-5 scores of the treatment group improved from 12.9±4.27 at baseline to 18±3.37, while no difference in IIEF scores was observed in the control group. All 20 patients in the treatment group reported improved erections, including erectile capabilities and improved intercourse success. Significant improvements were also observed in the SF-36 scores. Although the duration of action may be short due to easy exit from the corpora cavernosa, the stem cell-derived bioactive molecules from umbilical cord tissue without blood cells or blood products can become an off-the-shelf ED therapy if proven to be effective.

5.2. Autologous SC or bioactive factors used in ED therapy

5.2.1. Clinical trials with autologous bone marrow-derived mesenchymal stem cells (BM-MSCs)—

The BM-MSCs, known as non-hematopoietic stem cells (HSCs), are located in the medullary stroma of bone marrow. BM-MSCs represent a heterogeneous population that accounts for 1/10,000 to 1/100,000 cells in bone marrow tissue [60]. The yield of BM-MSCs is highly associated with the age and/or pathological conditions of the donors[61].

Yiou et al. (2016) conducted a study on intracavernous autologous BM-MSCs injections for post-radical prostatectomy (RP) ED (NCT01089387) [62]. In their first report, 12 patients were enrolled in a dose-escalating study (2×10^7, 2×10^8, 1×10^9, 2×10^9), and the results showed that spontaneous erections were significantly greater with the higher doses, and sexual function scores at 12 months were not significantly different from those at 6 months, suggesting a sustained beneficial effect of BM-MSCs injection. In the second report [63], 15 patients (9 patients from the first study and 6 additional patients) received the optimal dose identified in the first report. IIEF-5 scores, orgasmic function, overall satisfaction, and intercourse satisfaction were assessed. At 6 months, BM-MSC injection markedly improved the sexual scores compared to baseline of the additional six patients. Moreover, all patients reported that erections were sufficient for penetration in the presence of one erectogenic treatment (sildenafil or alprostadil). However, there was a decline in IIEF-erectile function after one year, suggesting the need for repeated injections.

Demour et al. (2018) examined the tolerability, safety, and efficacy of intracavernous autologous BM-MSCs injections for diabetic patients with ED (NCT02945462) [64]. Tolerability was assessed immediately and after 24 hours, while safety was evaluated for 2 years. Efficacy was assessed using IIEF-15 and Erection Hardness Score (EHS) for 12 months. Intracavernous autologous BM-MSCs were injected at baseline and 30 days later into four diabetic patients with ED. The authors reported improvements in EHS, IIEF-15

scores, sexual desire, intercourse satisfaction, and overall satisfaction in these four men with diabetic ED.

An open-label phase 1 trial of BM-MSCs for both post-prostatectomy ED and diabetes mellitus-associated ED patients was published in 2021 (NCT02344849) [42]. Ten ED patients, five with Post-radical prostatectomy ED (post RP-ED) and five with DM-associated ED who had failed to respond to maximal dosage of PDE5 inhibitors, received a single intracavernous injection of 3×10^7 autologous BM-MSCs into the corpus cavernosum. The safety and efficacy of this trial were assessed at 1, 3, 6, 9, and 12 months. Compared with the baseline, the IIEF score increased at the 1-month time point. The SEP and GAQ results showed a successful penetrative sex rate of 30–40% until 12 months after treatment. However, the peak systolic velocity (PSV) and end-diastolic velocity (EDV) showed no significant changes compared with baseline. Several patients experienced side effects, including pyrexia, prostatitis, pruritus, back pain, and hyperglycemia. Due to its invasiveness and cost, BM-MSC therapy is unlikely to be a treatment of choice for ED.

5.2.2. Clinical trials with autologous adipose-derived regenerative cells (ADRCs) also known as a stromal vascular fraction (SVF)—A stromal vascular fraction (SVF) is a heterogeneous group of cells that can be isolated from adipose tissue in a laboratory. The SVF is composed of several cell types including adipose-derived stem cells (ADSCs), preadipocytes, pericytes, lymphocytes, smooth muscle cells, macrophages, endothelial precursor cells, and endothelial cells. Due to their multipotency and desirable paracrine effects, SVF has been investigated as a potential treatment for various medical conditions [65].

Chalyy et al. (2016) conducted a study to evaluate the efficacy of SVF in treating vasculogenic erectile dysfunction in men (NCT02472431) [66]. Six men with an average age of 47±19 years and an IIEF-5 score of 13±5 were enrolled in the study. The workup revealed a low Erection Hardness Score (2±1.4), peak systolic velocity by penile color Doppler ultrasound (< 30 cm/sec), resistance index > 0.8, and absence of nocturnal penile tumescence. SVF was extracted from the patients using Cytori's Celution 800/CRS System via anterior abdominal wall and flank liposuction (liposuction volume 150–200 ml). The mean SVF cell count after preparation was 190 million cells/ml, which was then injected into the corpora cavernosa. The effectiveness and safety of the treatment were assessed at 1, 3, and 6 months after injection. After 6 months, all patients showed improvement in erectile function parameters, including IIEF scores, the Erection Hardness Score, SEP, and PSV. Moreover, all patients experienced morning erections after the treatment. The study demonstrated the potential of SVF as a safe and effective treatment for vasculogenic erectile dysfunction.

Post RP-ED is a significant concern for men following RP [67,68]. Animal studies have indicated that stem cell therapy may offer promising results for improved erectile function recovery after cavernous nerve injury[69]. Haahr et al. (2018) published an open-label, single-arm, single-center phase 1 study in 21 patients that followed them for 12 months, demonstrating the safety and efficacy of autologous adipose-derived regenerative cells (ADRCs) injection in men after RP (NCT02240823) [70]. The mean age of patients

was 60.2 years (range 46–69), and the mean time between RP and ADRCs treatment was 10.7 months (range 6–15 months). None of the 21 patients had responded to oral medication (phosphodiesterase type 5 inhibitor) or intracorporeal injections (alprostadil or aviptadil combined with phentolamine). Freshly isolated ADRCs were harvested from the lipoaspirate of the patient's subcutaneous fat. The ADRCs were isolated within 2 hours of lipoaspiration using the automated processing Celution® 800/CRS system (Cytori Therapeutics, San Diego, California, USA). The isolated ADRCs were aseptically recovered by gently resuspending in 5 mL Lactate Ringer's solution with a syringe. Using a 3-way stopcock, 1 mL ADRCs suspension was aseptically withdrawn for further in vitro characterization, while the remaining 4 mL cell suspension was re-injected into the patient's corpus cavernosum within 15 minutes. The injection dose varied due to differences in the subcutaneous fat available in each patient. Safety was the primary endpoint, while sexual function and urinary continence were secondary endpoints that were recorded at 1, 3, 6, and 12 months after ADRCs injection. No serious adverse events occurred, but eight minor events related to liposuction were noted but reversible. Median IIEF-5 scores significantly increased after 6 months in the continent group and were sustained at 12 months. Eight of the 15 continent patients reported sufficient erectile function for sexual intercourse. There were no improvements in erectile function in the group of incontinent men or among men with ED prior to RP. ADSC therapy is less invasive and costly as compared to BM-MSC therapy. Nevertheless, unless the efficacy can be markedly improved in further studies, ADSC therapy will not be as competitive as allogeneic stem cells or products derived from the placenta or umbilical cord.

5.2.3. Clinical trials with autologous adipose-derived stem cells and platelet lysate—Protegerou et al. (2019) conducted a pilot study to compare the efficacy of intracavernous injection of adipose-derived mesenchymal stem cells (ADMSCs) versus platelet lysate (PL) in the treatment of organic ED. Eight men were enrolled, with 5 receiving intracavernous injection of ADMSCs and 3 receiving PL alone. Adipose tissue obtained from lipoaspiration was processed to isolate stem cells, which were expanded in culture, and cells from passage 4 were suspended in 2 mL of PL for intracavernous injection. PL was obtained from 20 mL of the patient's peripheral venous blood to obtain platelet-rich plasma (PRP), which was stored at −80°C for 48 hours and thawed for injection. The combination therapy group received $38.9 \pm 14.4 \times 10^6$ ADMSCs in combination with 2.2 ± 0.3 mL of PL, while the other group received 2.3 ± 0.4 mL of PL only. The authors reported that most patients in both groups experienced increased IIEF-5 scores, morning erections, and improved peak systolic velocity, with effects lasting several months[71]. Theoretically, platelet lysate may enhance the effect of ADMSC but the combination is more invasive and costly than the allogeneic placenta or umbilical cord-derived stem cells and bioactive products. Moreover, studies with sham controls and adequately powered clinical trials are needed to determine the efficacy of this combination therapy for the ED [72].

6. Clinical trials currently in progress

There are several ongoing clinical trials investigating the use of stem cell therapy for ED, which aim to further evaluate the safety and efficacy of this treatment approach. Some of

the unique features of these trials include comparing the use of different stem cell types, delivery methods, evaluation of long-term outcomes, and patient selection criteria.

These ongoing clinical trials will add to the body of knowledge on the use of stem cell therapy for ED, by providing further insight into optimal stem cell types, delivery methods, and patient selection criteria for this treatment approach. This will also provide additional data on the safety and efficacy of stem cell therapy for ED, and help to establish it as a viable treatment option for patients with this condition. Table 2 displays ongoing clinical trials related to stem cell therapy and ED, retrieved from the United States National Institute of Health database and European Union Clinical Trials Registry using the search terms “stem cell” and “erectile dysfunction.”

7. Safety and side effects

Reported clinical trials have shown no serious adverse side effects in terms of safety assessments. Common side effects of stem cell injection include temporary mild pain, redness, bruising, or irritation at injection sites. No treatment-emergent adverse events (TEAEs) that resulted in death or dropout were reported during the clinical trials. However, some patients considered stem cell injections unduly burdensome and asked for the implantation of a penile prosthesis instead [63]. In the case of patients who developed ED after radical prostatectomy, there is no evidence of prostate cancer recurrence after stem cell injections [58].

8. Conclusion

The promising results of preclinical and clinical studies have generated considerable interest in SCT for ED. SCT has the potential to become a regenerative treatment option for ED patients who are unresponsive to PDE-5 inhibitors. The primary mechanism behind SCT’s ability to improve erectile function is likely due to paracrine effects, with engraftment and cellular differentiation playing an ancillary role. The optimal dosage, frequency, and maintenance schedule for SC therapy for ED have yet to be established [30]. Large-scale clinical trials with sham controls are necessary to assess the long-term safety and efficacy of SCT for ED. Additionally, the ethical considerations surrounding the application of SCs for men with ED remain challenging.

9. Expert opinion

Stem cell therapy has emerged as a promising therapeutic option for patients with ED. Although the therapy has limited success in tissue reconstruction and cell replacement its paracrine regenerative effect has been found to improve erectile function. MSCs from different sources have been studied, with BM-MSCs, ADSCs, and SVF being the most widely investigated. The harvesting of stem cells involves a minor surgical procedure under local anesthesia, with bone marrow or adipose tissue being processed according to various protocols. To prevent potential immune reactions, only autologous adult stem cells have been used in human clinical trials thus far.

Alternatively, the human placenta is an abundant source of stem cells, containing comparably young and healthy cells that are highly responsive to various stimuli. Human placental-derived stem cells have low rejection potential, making them an ideal candidate for allogeneic cell therapy. The mechanism behind the regenerative effects of hPSCs is still being studied, along with their potential applications in various types of ED[23]. Despite the advantages of hPSCs, it is important to note that the clinical use of these cells has raises ethical concerns. More studies are required to determine the potential benefits and risks of hPSC therapy for ED patients.

Many studies have demonstrated that there are overlaps of mechanisms for restorative therapies including stem cell therapy, shock wave therapy, and PRP therapy[73] [74] [75]. Some of the key signaling pathways that are targeted by these therapies include the vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), nitric oxide (NO), stromal cell-derived factor-1 (SDF-1), and mitogen-activated protein kinase (MAPK) et al. Several studies have investigated the combination of Li-ESWT with stem cell therapy for the treatment of ED. For example, a publication reported that combining Li-ESWT with ADSCs therapy resulted in a significant improvement in erectile function compared to Li-ESWT alone [76]. Another study reported in 2021 investigated the combination of Li-ESWT with bone marrow-derived stem cell therapy[77]. The study found that the combination therapy significantly improved erectile function and penile blood flow and resulted in the regeneration of penile tissue. The combination of Li-ESWT with PRP therapy has also been proposed as a potential treatment for ED [74] [73]. Although two conference abstracts reported benefits with combination therapy, the only published paper showed that the results of combination therapy were similar to Li-ESWT alone.

Restorative therapies for ED have shown promising results in preclinical and clinical studies [78]. However, there is still much to learn about the optimal protocol to maximize the safety and efficacy of SCT. The optimal dosage and frequency of stem cell therapy for ED have not been established, and larger clinical trials with longer follow-up periods are needed to evaluate their safety and efficacy. Further research into stem cell therapy for ED, an increasingly more common disorder, is essential to identify the most effective and safe approaches for treating patients who do not respond to conventional therapies. Furthermore, ethical concerns surrounding the use of stem cells for ED treatment exist, and careful consideration must be taken to ensure the safety and welfare of patients.

In summary, while stem cell therapy for ED shows promise, further research is necessary to optimize its use and ensure its safety and efficacy. Nevertheless, the potential of stem cells in the treatment of ED is an exciting development that holds great promise for the future of ED therapy.

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Article highlights

- Erectile dysfunction (ED) affects a significant proportion of men worldwide and has a major impact on quality of life.
- Traditional treatments for ED, such as phosphodiesterase type 5 inhibitors (PDE5i), have limitations and may not be effective in all patients.
- Stem cell therapy (SCT) represents a promising new approach to the treatment of ED.
- Preclinical studies have shown that stem cell therapy can improve erectile function through a variety of mechanisms, including neovascularization and nerve regeneration.
- Stem cell therapy represents a promising new approach to the treatment of ED, with the potential to improve erectile function in patients who do not respond to traditional treatments.
- Further research is needed to optimize the use of stem cells, stem cell products, or combination therapies for the treatment of ED and to determine the long-term safety and efficacy of this approach.

Table 1.

Summary of clinical studies of SCT for ED only studies found in the United States National Institute of Health database and European Union Clinical Trials Registry were included)

Ref No.	Authors	Cause/type of ED	Study type	Stem cells	Clinical trial identifier	Key outcomes	Publication date
[42]	You et al.	Post-prostatectomy ED (5 patients) and diabetic mellitus-associated ED (5 patients)	open label phase 1	BM-MSCs 3×10^7 cells	NCT02344849	No TEAEs were thought to be related to SCT. Significant improvements in erectile function and patient satisfaction.	2021
[57]	Al Demour et al.	Diabetic ED (refractory ED)	Phase 1/2	WJ-MSCs 2×10^7(2 times with a 30-day interval, first at baseline)	NCT02945449	No serious side effects except mild pain during injection. Significant improvements in IIEF-5, EHS, PSV basal and 20min PSV.	2022
[58]	Levy et al.	Chronic organic ED	Phase 1, Open label, nonrandomized, single center	PM-MSC Not quantified	NCT02398370	3/8 patients reported irritation at injection sites. Significant increases in PSV.	2016
[64]	Al Demour et al.	Diabetic ED	Phase 1 pilot, open label, single arm and single center	BM-MSCs 30×10^6 cells(one at baseline, the second at day-30)	NCT02945462	No significant adverse side effects. Dramatical improvement of IIEF-15 and EHS.	2018
[66]	Chalyy et al.	Organic ED (vasculogenic ED)	Phase 1 and 2	Autologous stromal vascular fraction (SVF) of adipose tissue	NCT02472431	No adverse effects. Significant improvement in erectile function and all patients experienced spontaneous morning erections after treatment.	2016
[70]	Haahr et al.	ED after Post radical prostatectomy	Open label, phase 1 clinical trial	ADRCs	NCT02240823	No side effects. Media IIEF-5 scores and erectile function significantly increasing for continent patients.	2018
[71]	Protogerou et al.	Organic ED	Pilot study	ADMSCs $38.9\pm14.4\times10^6$		No severe adverse reactions. Erectile function was improved for all patients, including IIEF-5, PSV.	2019
[72]	Protogerou et al.	Organic ED	Phase 1, single center pilot study	ADSCs (9.5, 43.2, 37.2, 53.2, $51.4)\times10^6$	Approved by Scientific Committee of Attikon Hospital	No side effects, except a minor pain in the penis during injections. Some improvement in erectile function.	2020

ED: Erectile dysfunction; 2) BM-MSCs: bone marrow-derived mesenchymal stem cells; 3) WJ-MSCs: Wharton's Jelly-derived mesenchymal stem cells; 4) PM-MSC: placental matrix-derived mesenchymal stem cells; 5) ADRCs: adipose-derived regenerative cells; 6) ADMSCs: adipose-derived mesenchymal stem cells 7) ADSCs: autologous adipose-derived stem cells.

Table 2.

Overview of completed/ongoing clinical trials of SCT for ED (registered completed or ongoing trials without published results)

	Status	Clinical trial identifier	Intervention/treatment	Location
1	Completed in 2021, full results awaited	2015–005140-33	Fat derived stem cells (SVF) for ED after prostatectomy	Denmark
2	Completed in 2019 Full results awaited	NCT03751735	Wharton Jelly mesenchymal stem cells (WJ-MSCs) for diabetic ED	Jordan
3	Recruiting Estimated completion in 2023	NCT04972890	Umbilical cord mesenchymal stem cells (placebo) for ED with DM, phase 2 and phase 3	Indonesia
4	Recruiting Estimated completion in 2023	NCT04594850	Mesenchymal stem cells for ED, phase 2	Pharmicell Co., Ltd.
5	Recruiting, estimated completion in 2025	NCT05147779	Allogeneic adult umbilical cord derived mesenchymal stem cells(hUC-MSCs) for Peyronie's disease	Medical surgical associates center, St. John's, Antigua and Barbuda
6	Recruiting, estimated completion in 2025	NCT03933995	5-year long-term follow up study of the clinical trial NCT02344849 (BM-MSCs injection for ED)	Pharmicell Co., Ltd.
7	Unknown	NCT03361631	Autologous bone marrow derived mesenchymal stem cells for ED with DM type 1, phase 1	France
8	Unknown	NCT02414308	Adipose tissue stem cell injection for ED associated with Peyronie' disease	Egypt
9	Unknown	NCT02648386	NeuroGegen scaffold/BMMCs transplantation for ED after rectal cancer surgery, phase1 and phase 2	Nanjing, China
10	Unknown	NCT02240823	Adipose derived stem cells for ED patients after prostatectomy, phase 1	Denmark
11	Unknown	NCT02665520	Liposuction for retrieval of own stem cells from fat cells for ED, phase 1	Saudi Arabia
12	Unknown	NCT02745808	Injection hUC-MSC and injectable Collagen Scaffold for ED with DM	Nanjing, China