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REVIEW

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The promise of mesenchymal stromal/stem cells in erectile dysfunction treatment: a review of current insights and future directions

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Abstract

Erectile dysfunction is a common and multifactorial condition that significantly impacts men's quality of life. Traditional treatments, such as phosphodiesterase type 5 inhibitors (PDE5i), often fail to provide lasting benefits, particularly in patients with underlying health conditions. In recent years, regenerative medicine, particularly stem cell therapies, has emerged as a promising alternative for managing erectile dysfunction. This review explores the potential of mesenchymal stromal/stem cells (MSCs) and their paracrine effects, including extracellular vesicles (EVs), in the treatment of erectile dysfunction. MSCs have shown remarkable potential in promoting tissue repair, reducing inflammation, and regenerating smooth muscle cells, offering therapeutic benefits in models of erectile dysfunction. Clinical trials have demonstrated positive outcomes in improving erectile function and other clinical parameters. This review highlights the promise of MSC therapy for erectile dysfunction, discusses existing challenges, and emphasizes the need for continued research to refine these therapies and improve long-term patient outcomes.

Keywords MSCs, Male infertility, Erectile dysfunction, Stem cell therapy, Regeneration, Exosomes

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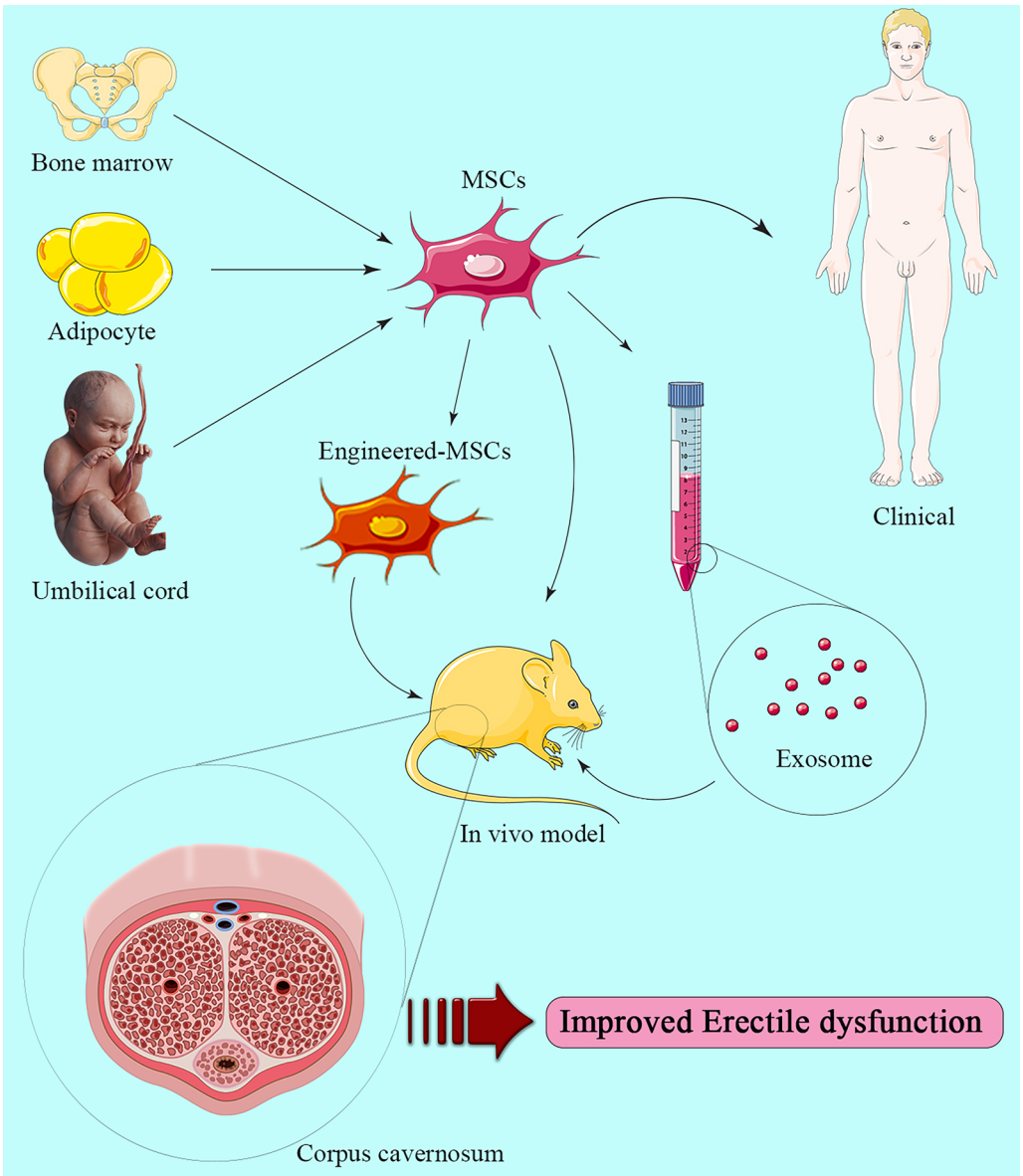
Graphical abstract



Introduction

Erectile dysfunction is a prevalent condition that significantly affects the quality of life for millions of men worldwide, often leading to profound emotional and psychological challenges [1, 2]. The causes of erectile dysfunction are multifaceted, stemming from intricate interactions between vascular, neurological, hormonal, and psychological systems. Common contributors include impaired blood flow, nerve damage, hormonal imbalances, and mental health issues, with conditions like diabetes, high blood pressure, and post-prostate surgery complications further compounding its impact [3, 4]. Vascular factors, such as reduced blood circulation resulting from atherosclerosis or endothelial dysfunction, represent the predominant causes, responsible for approximately 60% of cases [5]. Neurological elements, including nerve injury resulting from spinal cord trauma, account for 10–19% of instances [6]. Furthermore, hormonal imbalances, including reduced testosterone levels, are involved in around 10–20% of cases [7]. Research

has also identified several clinical factors contributing to the development of erectile dysfunction in men. These include accidental injury to the penile cavernous nerve during surgery, adverse chemical side effects, traumatic injury to genital tissue, underlying endocrine dysfunction, and fibrosis in penile vascular smooth muscle tissue. Even though these factors are not as prevalent as vascular and neurological causes, they are essential in interfering with the intricate physiological mechanisms necessary for normal erectile function, especially in certain subgroups of patients experiencing severe or multifactorial issues [8]. While traditional treatments such as phosphodiesterase type 5 inhibitors (PDE5i), penile implants, and vacuum devices are widely available, they often fail to address the root causes of erectile dysfunction. Moreover, these treatments can be insufficient for patients with complex or severe underlying conditions, leaving a gap in effective and sustainable management strategies [9, 10].

Recent advancements in regenerative medicine offer new hope for addressing the underlying causes of erectile dysfunction rather than merely alleviating symptoms. Among these, mesenchymal stromal/stem cells (MSCs) have emerged as a promising therapeutic tool due to their remarkable ability to repair tissue, reduce inflammation, and promote cellular regeneration. Much of this therapeutic potential stems from the paracrine signaling of MSCs, particularly through the secretion of exosomes—tiny, bioactive vesicles loaded with proteins, lipids, and RNAs that facilitate tissue healing and cellular communication [11]. MSC-derived exosomes, in particular, have shown promise in preclinical studies, demonstrating the ability to regenerate smooth muscle cells, enhance endothelial function, and reduce inflammation, all of which are critical for restoring normal erectile function [12, 13].

This review seeks to provide a clear and comprehensive understanding of the advancements in MSC therapy for erectile dysfunction. We explore the mechanisms behind their regenerative effects, evaluate current clinical findings, and discuss the challenges that must be addressed to unlock their full potential. By highlighting both the promise and the limitations of these therapies, this review underscores the transformative possibilities of regenerative medicine in reshaping erectile dysfunction treatment and improving patient outcomes.

Mesenchymal stromal/stem cell: origin, properties, and therapeutic application

MSCs represent a class of multipotent cells capable of giving rise to various cell types. They are distributed across a diverse range of human tissues, including bone marrow (BM), adipose tissue (AD), umbilical cord (UC), and menstrual blood [14–17]. First identified within BM [18], MSCs have since been isolated from numerous sources, each with varying yields and purity [19]. Adipose tissue generally offers a greater yield of MSCs compared to bone marrow, whereas MSCs derived from umbilical cords show superior proliferative capacity and purity [20]. These distinctions may profoundly affect their therapeutic capabilities, particularly in relation to erectile dysfunction. MSCs obtained from AD are commonly favored because of their plentiful availability and straightforward extraction, while BMMSCs are regarded as the benchmark due to their thorough investigation in scientific studies [21, 22]. Nonetheless, UC-MSCs are receiving growing interest due to their ability to modulate the immune system and the reduced ethical issues associated with their use [23]. These variations based on the source highlight the significance of choosing the right type of MSC to enhance therapeutic results in erectile dysfunction. The discovery of MSCs opened new avenues for regenerative medicine and cellular therapies due to their remarkable ability to modulate tissue repair processes. Recognizing the need to standardize MSC characterization, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) formally defined MSCs in 2006 based on specific criteria: MSCs must exhibit plastic adherence in culture, express CD105, CD73, and CD90 while lacking expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR, and they must have the capacity to differentiate into osteoblasts, adipocytes, and chondroblasts under laboratory conditions [24–28].

Notably, MSCs derived from various tissues possess unique properties in terms of isolation efficiency, cellular phenotype, growth rates, and differentiation potential, yet they retain common core characteristics with BM-derived MSCs, including self-renewal and multipotent differentiation [20, 29]. This consistency across different sources supports their utility across a wide range of clinical applications, particularly in regenerative medicine. However, over recent years, research has evolved from viewing MSCs as simple building blocks for tissue repair to recognizing them as potent modulators of the local tissue environment through mechanisms that extend beyond direct cellular differentiation [30].

Current research suggests that MSCs exert their therapeutic effects largely through paracrine mechanisms, secreting a spectrum of biologically active molecules that influence surrounding cells in damaged tissues. These secreted factors include cytokines, chemokines, growth factors, and EVs [31]. EVs, in particular, have emerged as central players in MSC-mediated repair, carrying molecular signals that can influence cell behavior, modulate immune responses, and guide tissue regeneration. This shift in understanding—from MSCs as cells that directly

replace damaged tissue to cells that orchestrate healing through signaling—has prompted some experts to advocate for renaming MSCs as "medicinal signaling cells," emphasizing their indirect yet powerful role in promoting healing [32].

The versatility of MSCs has also led to the development of innovative "acellular therapies," which capitalize on MSC-derived products rather than the cells themselves. These acellular therapies, relying on the potent biological secretions of MSCs, have shown promise in promoting tissue repair without the complexities associated with live-cell therapies. This approach highlights a new frontier in regenerative medicine, where MSC-derived secretions, rather than the cells themselves, become the primary agents of therapeutic intervention, opening opportunities for safer and more accessible treatments [33, 34].

Extracellular vesicles: classification, biological functions, and therapeutic potential

EVs are a highly versatile and dynamic group of membrane-bound particles released naturally by nearly all cell types, playing crucial roles in intercellular communication [35]. This diverse category includes exosomes, microvesicles (MVs), microparticles, ectosomes, apoptotic bodies, oncosomes, and other vesicles, each differing in origin, size, and functional properties. Enveloped by a lipid bilayer, EVs cannot replicate but act as vehicles, carrying a variety of molecular cargo—proteins, nucleic acids (DNA, RNA, miRNAs), lipids, and metabolites—that influence nearby and distant cells through paracrine signaling [36, 37]. As research uncovers their significance, EVs are increasingly recognized as vital players in regulating physiological and pathological processes, and their stability in biofluids like blood, urine, and saliva underscores their diagnostic and therapeutic potential [38].

Exosomes, a subtype of EVs, are particularly notable for their distinctive origin and molecular composition. These nano-sized vesicles (30–150 nm in diameter) arise from the endosomal pathway within cells, forming intraluminal vesicles inside multivesicular bodies (MVBs) [39]. When MVBs fuse with the plasma membrane, exosomes are released into the extracellular space. Exosomes are readily identifiable by their "cup" or "dish" shape under electron microscopy and by specific markers on their surface—most notably tetraspanins (CD9, CD63, CD81), along with heat shock proteins (Hsp60, Hsp70, Hsp90) and proteins involved in membrane transport, like Rab GTPases. Exosome cargo also includes unique lipids and metabolic enzymes, which play essential roles in their bioactivity. Due to their capacity to carry and deliver specific biomolecules, exosomes are heavily investigated as potential biomarkers in diagnostics and as carriers for targeted drug delivery, capitalizing on their natural ability to transport therapeutic agents across cell barriers [40, 41].

MVs, or ectosomes, are another important EV subtype. Slightly larger than exosomes (100–1000 nm), MVs are generated through outward budding from the plasma membrane and are released in response to various cellular stimuli [39]. They carry a distinct phosphatidylserine-rich membrane that binds annexin V, which can facilitate the interaction of MVs with specific cell types [42]. MVs serve essential roles in cellular processes such as coagulation, immune responses, and cell signaling pathways. This function is particularly critical in disease contexts where MVs can interact with endothelial cells, influencing inflammatory and thrombotic responses. Their dynamic cargo, which can vary based on the parent cell type and cellular conditions, makes MVs powerful messengers capable of inducing significant physiological changes in target cells [38, 43].

Apoptotic bodies (ABs) are the largest category of EVs (1–5 μm) released during the programmed cell death process. Unlike exosomes and microvesicles, ABs contain cellular organelles, fragmented DNA, and nuclear components enclosed within a membrane [44]. Their formation is regulated by caspase-3 activation of the ROCK-1 pathway, facilitating the detachment of cellular fragments. ABs are quickly recognized and phagocytosed by immune cells, thus preventing necrosis and subsequent inflammatory responses. This clearance mechanism highlights the role of ABs in immune regulation and maintenance of tissue health [45, 46].

Notably, EVs, which include exosomes and other nano-sized particles derived from MSCs, show potential as a safer alternative to direct MSC transplantation. Because EVs carry the bioactive molecules of MSCs without the risk of unwanted differentiation or immune rejection, they represent a promising cell-free therapeutic option for conditions such as skin wounds, bone injuries, and cartilage degeneration. Researchers have explored MSC-derived EVs from various tissue sources, including BM, AD, UC, and placenta, demonstrating their broad applicability in preclinical models of degenerative diseases and immune-related conditions [47, 48].

Despite the promise of EV-based therapies, there are still obstacles to their clinical application, especially in the areas of EV isolation, purification, and storage. Existing isolation techniques, like ultracentrifugation and size-exclusion chromatography, require considerable labor and may lead to low yields or contamination with non-vesicular materials [49]. Protocols for purification should also guarantee the elimination of proteins and other contaminants to obtain high-quality EV preparations. Additionally, it is essential to preserve the stability

and bioactivity of EVs during storage, as cycles of freezing and thawing can impact their therapeutic effectiveness [50, 51]. Recent progress, such as the creation of tangential flow filtration systems and uniform cryopreservation methods, seeks to tackle these issues and enhance consistency in EV production. New strategies, including scalable bioreactor systems for EV generation and synthetic EV mimetics, are being investigated to improve their suitability for clinical use [52–55].

The therapeutic effect of mscs on erectile dysfunction

ADMSCs in erectile dysfunction

AD is one of the most efficacious sources of MSCs. ADMSCs are active cells that block apoptosis, promote revascularisation of damaged regions, and modulate immunological responses [56, 57]. According to research, ADMSCs are a form of adult multipotent stem cells distinguished by their ability to self-renew and differentiate. ADMSCs can be acquired through minimally invasive methods that do not cause harm to the host organism. Moreover, the success of allogeneic stem cell transplantation provides valuable insights into the restricted immunogenic response associated with these cells [58, 59].

Gu et al. [60] conducted a study in which they administered ADMSCs to neurovascular injured erectile dysfunction rat models. ADMSC therapy improved erectile function and mitigated the histological alterations three months following pelvic neurovascular injury in vivo, suggesting that MSC transplantation could potentially enhance long-term outcomes in neurogenic, myogenic, and vascular tissues. Zhai et al. investigated the application of ADMSCs derived mitochondria transplantation in rat models of cavernous nerve injury erectile dysfunction [61]. The transplantation of ADMSCs-mitochondria significantly improved erectile function and increased smooth muscle content in rats with cavernous nerve injury-induced erectile dysfunction. Furthermore, there was a decrease in the levels of reactive oxygen species (ROS), mitochondrial reactive oxygen species (mtROS), and cleaved caspase 3, while an increase was observed in the levels of superoxide dismutase (SOD) and ATP following the transplantation of ADMSCs -mitochondria. The mitochondrial structure of cells within penile tissues was compromised in rats with cavernous nerve injury-induced erectile dysfunction. ADMSCs have the capability to transfer their mitochondria to the smooth muscle cells of the corpus cavernosum. The application of ADMSCs prior to treatment demonstrated a notable reduction in the rates of apoptosis, levels of ROS, and mtROS while also facilitating the restoration of ATP levels in corpus cavernosum smooth muscle cells.

Peroxiredoxin 2 (PRDX2) belongs to the peroxidase family and demonstrates therapeutic effects through the inhibition of ROS and ferroptosis. It is anticipated that PRDX2 will augment the therapeutic efficacy of ADMSCs in the treatment of neurogenic erectile dysfunction [62, 63]. Chen et al. [64] demonstrated that PRDX2 has a notable effect on enhancing the viability of ADMSCs by inhibiting apoptosis and ROS in H2O2-stimulated ADMSCs. The findings indicated that the overexpression of PRDX2 in ADMSCs reduced oxidative stress in H2O2-stimulated corpus cavernosum smooth muscle cells and inhibited ferroptosis in RSL3-stimulated corpus cavernosum smooth muscle cells. This was evidenced by a decrease in ROS, total iron content, and MDA, alongside an increase in SOD and GSH, as well as alterations in the expression of ferroptosis-related proteins GPX4 and ACSL4 (Fig. 1).

Neuregulin-1 (NRG1) serves as a critical component in the process of nerve repair and provides protective benefits for blood vessels and smooth muscle, positioning it as a potential target for the treatment of nerve-related erectile dysfunction. The NRG1/ErbB signaling pathway plays a vital role in the growth and repair of neural tissue, regulating fundamental processes such as neuron migration, differentiation, and myelination. In peripheral nerves, NRG1 facilitates recovery through the regulation of Schwann cell activity. Furthermore, NRG1 contributes to the maintenance and regeneration of blood vessels through the inhibition of the RhoA and Rock1 pathways [65, 66]. The characteristics of NRG1 suggest its potential as a target for gene transfection, aimed at enhancing the therapeutic efficacy of ADMSCs in the treatment of erectile dysfunction associated with cavernous nerve injury. Cheng et al. [67] engineered ADMSCs to overexpress NRG1 by employing superparamagnetic iron oxide nanoparticle (SPION)-based encapsulation of NRG1, aiming to potentiate the therapeutic efficacy of ADMSCs in treating nerve injury-related erectile dysfunction. This work is limited by its in vitro approach and requires further in vivo assessment.

Another study investigated the secretion of insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) by ADMSCs. In a two-week study, aged rats treated with ADMSCs showed improved erectile function, increased IGF-1, bFGF, and VEGF levels, and partial restoration of cavernous smooth muscle and endothelium compared to untreated aged rats and young controls. Cell experiments with neutralizing antibodies further indicated that these growth factors enhance cavernous smooth muscle survival. Overall, these findings suggest that ADMSCs may improve aging-related ED through the secretion of key

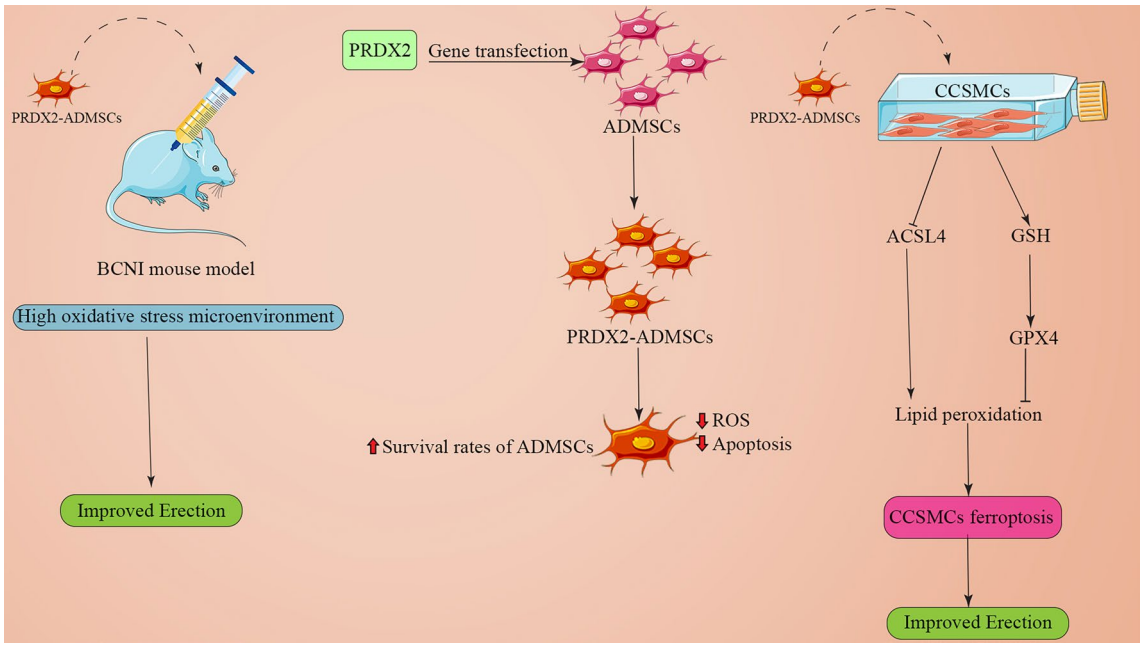


Fig. 1 Role of PRDX2 in enhancing the viability and functionality of ADMSCs and corpus cavernosum smooth muscle cells under oxidative and ferroptotic stress. PRDX2 overexpression in ADMSCs improves cell viability by reducing apoptosis and ROS levels in H2O2-stimulated cells. Additionally, PRDX2 alleviates oxidative stress and ferroptosis in H2O2- and RSL3-stimulated corpus cavernosum smooth muscle cells by decreasing ROS, total iron content, and MDA, while increasing SOD activity, GSH levels, and GPX4 expression, and reducing ACSL4 expression

growth factors, supporting their therapeutic potential [68].

In summary, ADMSCs show potential as a therapy for erectile dysfunction by promoting nerve repair, reducing oxidative stress, and preserving smooth muscle. Key growth factors and modifications, such as NRG1 overexpression, enhance their efficacy, supporting ADMSCs as a promising approach for treating ED, though further in vivo research is needed for confirmation.

BMMSCs in erectile dysfunction

Matsuda et al. performed a study to evaluate the impact of BMMSCs on erectile dysfunction subsequent to cavernous nerve injury in rats [69]. The results indicate that BMMSCs exert a therapeutic impact on nerve injury by enhancing functional and structural indicators in the recovery of erectile function. The MSC-treated group exhibited superior preservation of intracavernous pressure, a measure of erectile function relative to controls, and an elevated smooth muscle-to-collagen ratio, essential for maintaining healthy tissue structure. The increased quantity of FluoroGold-positive neurons in the major pelvic ganglia (MPGs) suggests improved neuronal regeneration or maintenance. The identification of MSCs in the MPGs and wounded cavernous nerves indicates successful targeting of damaged areas, potentially aiding in repair. Furthermore, increased concentrations of neurotrophic factors, including brain-derived and glial cell-derived neurotrophic factors in the MPGs, suggest that MSCs may provide neuroprotective and neuroregenerative benefits, facilitating tissue restoration following nerve damage. These results underscore the potential of MSCs in restoring nerve function and tissue integrity in therapy for erectile dysfunction [69]. Another study conducted by Kim et al. [70] examined the role of BMMSCs conditioned medium (CM) in the treatment of erectile dysfunction. The study demonstrated that BMMSC-CM contains a diverse array of factors involved in angiogenesis, neuroprotection, and inflammation modulation. The therapeutic effects of this CM were validated in a rat model with cavernous nerve injury, where it exhibited both angiogenic and neurotrophic benefits. Notably, these effects were found to be dependent on the dose of CM administered. These results highlight the significant therapeutic potential of BMMSC-CM for treating erectile dysfunction. Moving forward, additional research will focus on refining methods to optimize the therapeutic impact of BMMSC-CM.

Multiple studies have emphasized the protective action of the transcription factor Nrf2 in many pathological situations, including erectile dysfunction associated with diabetes mellitus [71, 72]. Nrf2, a redox-sensitive transcription factor, modulates cellular redox equilibrium in reaction to detrimental stimuli [73]. Under normal

conditions, Nrf2 is tethered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1) [74]. During oxidative stress, Nrf2 separates from Keap1, moves to the nucleus, and activates genes related to oxidative resistance [75]. Nrf2 activation exhibits anti-apoptotic properties and may also modulate autophagy, thereby augmenting its protective function [76]. Wang et al. tested the effects of combining oral probucol with BMMSCs in diabetic rats to treat diabetic mellitus-induced erectile dysfunction, focusing on probucol's antioxidative, anti-apoptotic, and autophagy-promoting properties while also investigating potential underlying mechanisms [77]. The combination of probucol and BMMSC transplantation significantly improved erectile function, reduced fibrosis, and enhanced endothelial function compared to BMMSC transplantation alone. Probucol increased the expression of Nrf2 and HO-1, protecting against oxidative stress. It also reduced apoptosis by lowering Bax and Caspase3 levels while boosting Bcl-2 expression via the Nrf2 pathway. Additionally, probucol promoted autophagy in a dose-dependent manner, supporting cellular repair without inhibiting autophagic flux. These findings suggest that probucol enhances BMMSC transplantation, making it a promising treatment for erectile dysfunction.

Extracellular matrix (ECM) plays a key role in neural differentiation by influencing cell behavior through physical and biochemical ways, impacting processes such as adhesion, migration, and gene expression [78, 79]. Building on this, a recent study has investigated the use of a biomechanical ECM patch made from decellularized human fibroblast-derived ECM and PVA hydrogel combined with BMMSCs in a rat model of cavernous nerve injury. Results showed that the ECM patch significantly promoted neural development, smooth muscle regeneration, and nitric oxide production, leading to improved erectile function, highlighting its potential for restoring erectile function after prostatectomy [80].

In a notable study, Shan et al. examined the synergistic effects of low-energy shock-wave therapy (LESWT) in combination with BMMSC transplantation for enhancing erectile function in diabetic rats [81]. LESWT was shown to elevate SDF-1 levels, which facilitated the retention of transplanted BMMSCs within the cavernous body, thereby reducing their migration and promoting successful cell integration. Additionally, LESWT improved revascularization within the cavernous tissue, fostering an environment conducive to BMMSC survival. This combined approach significantly outperformed either therapy alone in restoring erectile function, indicating its potential as an effective therapeutic strategy.

Fang et al. investigated the combined transplantation of BMMSCs and endothelial progenitor cells (EPCs) for restoring erectile function in a rat model of cavernous nerve injury. The study revealed that co-transplantation significantly enhanced erectile function, as indicated by increased intracavernous pressure and improved histology of the corpus cavernosum. This combined approach not only boosted endothelial and smooth muscle content but also reduced apoptosis and elevated neuronal nitric oxide synthase (nNOS) expression. The co-culture of BMMSCs and EPCs led to a synergistic increase in neurotrophic factors, such as VEGF and nerve growth factor (NGF), further improving nerve regeneration. These findings underscore the potential of MSC and EPC co-transplantation as a superior therapeutic strategy for erectile dysfunction following cavernous nerve injury.

UC-MSCs in erectile dysfunction

The UC, typically discarded as medical waste post-birth, offers an ethically accessible, non-invasive source for MSCs (UC-MSCs). Like other MSCs, these cells possess remarkable self-renewal and multipotency, differentiating into various cell types (e.g., osteocytes, hepatocytes, neurons) [82]. UC-MSCs' unique properties—rapid self-renewal, minimal tumor risk, low immune rejection potential, and ease of production—make them a promising tool in regenerative medicine and immunotherapy [82].

In their study, Wang and colleagues evaluated the therapeutic effects of UC-MSCs on diabetes-related erectile dysfunction in a type 1 diabetic rat model. Results indicated that UC-MSC therapy improved erectile function by restoring intracavernous pressure and enhanced the smooth muscle-to-collagen ratio in penile tissue. Moreover, UC-MSC treatment appeared to inhibit TLR4 expression and boost VEGF and NOS levels, potentially reducing fibrosis and supporting vascular health in diabetes-induced erectile dysfunction [83]. Similarly, Mukti et al. investigated the potential of UC-MSCs to address erectile dysfunction in streptozotocin-induced diabetic rats [84]. By injecting diabetic rats with UC-MSCs, the study demonstrated a reduction in fibrosis and oxidative stress markers (TGF-β, α-SMA, and collagen) and an increase in muscle cell health and structural integrity. These results indicate that UC-MSCs may hold promise as a therapeutic approach for diabetes-associated erectile dysfunction by helping restore the tissue health essential for erectile function. A limitation of this study is that they did not assess the IL-10 secretion by MSCs, which is important for understanding their potential anti-inflammatory effects. Additionally, they did not evaluate SMAD pathway activation, a key indicator of fibrosis, in the diabetes-associated erectile dysfunction rats. Future research exploring the role of IL-10 from MSCs in regulating the SMAD pathways could provide deeper insights

into the therapeutic mechanisms involved in treating erectile dysfunction.

Feng et al. [85] investigated the effectiveness of UC-MSCs in addressing erectile dysfunction linked to type 1 and type 2 diabetes in rat models. The study involved administering UC-MSCs either via corpus cavernosum or tail vein injections, both of which showed similar results in enhancing erectile function. The findings revealed that UC-MSCs promoted smooth muscle growth, reduced collagen accumulation, mitigated oxidative stress, and countered diabetes-induced ferroptosis in corpus cavernosum smooth muscle cells. Additionally, UC-MSCs improved mitochondrial health and upregulated ferroptosis-inhibitory genes, supporting their potential to treat diabetes-related erectile dysfunction. This study has some limitations that require further investigation. While UC-MSCs show promise for treating diabetes-related erectile dysfunction, more research is needed to assess their safety, efficacy, and ideal dosage before clinical application. Additionally, although UC-MSCs release various molecules that aid their paracrine effects, the specific pathways by which they prevent ferroptosis in corpus cavernosum smooth muscle cells remain unclear.

Another study evaluated erectile function and the expression of key growth factors, including VEGF, bFGF, eNOS, and IGF1, over a 4-week period. In the STZ-induced diabetic rat model, erectile dysfunction, as indicated by intracavernous pressure (ICP), was significantly impaired. However, treatment with human Wharton's jelly MSCs (hWJ-MSCs) led to a significant improvement. The expression levels of VEGF, eNOS, IGF1, and bFGF were notably higher at the injection sites of hWJ-MSCs compared to the control group. These findings suggest that hWJ-MSC transplantation may improve erectile function in diabetic rats by enhancing the production of paracrine growth factors, offering a promising new therapeutic approach for erectile dysfunction [86].

As research progresses, UC-MSCs could emerge as a groundbreaking treatment, offering new hope for individuals suffering from erectile dysfunction and other conditions related to tissue degeneration.

Engineered MSCs in erectile dysfunction

MSCs and EVs obtained from MSCs can be optimized using a range of sophisticated methods, such as genetic engineering, surface modification, and tissue engineering, to enhance their ability to target specific sites and increase their therapeutic effectiveness. Among these methods, genetic engineering stands out as a robust strategy to enhance their therapeutic capabilities. Through the genetic modification of MSCs and MSC-exosomes to promote the expression of targeted proteins and soluble factors—like growth factors, cytokines, transcription factors, chemokines, enzymes, and microRNAs—there is a substantial enhancement of their inherent characteristics, such as survival, migration, and therapeutic efficacy. Genetic modifications can be accomplished through a variety of delivery methods, including both viral and non-viral approaches [87].

In a study by Liu et al. [88], the effectiveness of BMMSCs transfected with a lentivirus overexpressing miR-145 in treating erectile dysfunction was assessed. The administration of miR-145-engineered BMMSCs resulted in a marked improvement in erectile dysfunction. This improvement was accompanied by a notable increase in smooth muscle content within the penile tissues of erectile dysfunction-induced rats. In addition, the expression levels of α-SMA, desmin, and SM-MHC were significantly higher, while the levels of collagen 1, MMP2, and p-Smad2 were markedly decreased. The findings indicated that BMMSCs overexpressing miR-145 demonstrate their therapeutic impact by enhancing smooth muscle cells, a process regulated by TGF-β signaling that leads to the downregulation of collagen 1 and MMP2.

Studies have shown that a magnetic field-assisted nanotechnology-based technique can successfully retain cells within the corpus cavernosum, highlighting the potential for achieving therapeutic efficacy with low-dose injections [89]. Wu and colleagues conducted a study utilizing a reduced dosage of ADMSCs for intracavernous injection alongside a nanotechnology approach [90]. The research emphasized that low-dose ADMSC transplantation possesses considerable therapeutic promise, which is further amplified by the application of nanotechnology. The findings demonstrated a notable restoration of smooth muscle, endothelial, and nerve tissues in the group treated with ADMSCs, with even more pronounced enhancements noted when nanotechnology was utilized. The results indicated that nanotechnology significantly boosts the effectiveness of low-dose ADMSC therapy in enhancing erectile function, probably by facilitating tissue regeneration, and that NanoADMSCs persist in the corpus cavernosum for a minimum of three days following treatment.

Recent research indicated that increased production of stromal cell-derived factor-1 (SDF-1) in animal models with cavernous nerve injury-induced erectile dysfunction may enhance the condition of erectile dysfunction [91]. Furthermore, Yamaguchi et al. [92] highlighted the role of SDF-1 in promoting the recruitment of endothelial progenitor cells and facilitating angiogenesis. Building on these findings, Jeon et al. [93] investigated the effects of engineered MSCs overexpressing SDF-1 in the corpus cavernosum of a STZ-induced diabetic rat model of erectile dysfunction. The study indicated that SDF-1-engineered MSCs effectively ameliorated erectile dysfunction

in a diabetic rat model. These cells facilitated the restoration of erectile function by augmenting smooth muscle content in the corpus cavernosum and elevating the production of nNOS, eNOS, VEGF, and bFGF. The activation of the PI3K-AKT pathway in the corpus cavernosum was noted, possibly induced by VEGF. This pathway seemed to enhance cell survival by increasing Bcl-2 levels and decreasing Bax levels, therefore improving the viability of transplanted MSCs (Fig. 2). SDF-1-engineered MSCs demonstrated anti-apoptotic properties, enhancing their capacity to facilitate tissue repair and augment erectile function. Shin et al. [94] conducted a study to evaluate the combined effects of extracorporeal shock wave therapy and engineered MSCs overexpressing SDF-1 on improving erectile dysfunction in STZ-induced diabetic rats. The research highlighted that the combination of extracorporeal shock wave therapy with SDF-1-engineered MSCs proved more effective in treating erectile dysfunction than either therapy alone. This combined approach led to a notable increase in α-SMA, signifying better smooth muscle regeneration and enhanced tissue healing in the injured corpus cavernosum. Moreover, higher levels of NO and cGMP were observed with the combined treatment, facilitating vascular smooth muscle relaxation and further aiding in the recovery of erectile function.

Another study was conducted to evaluate the therapeutic potential of transplanting Bcl-2-modified BMMSCs for the treatment of diabetes mellitus-induced erectile dysfunction [95]. The study found that in the group treated with Bcl-2-modified BMMSCs, indicators of erectile function, including average erection frequency, erection rate, peak intracavernous pressure, and the ratio of peak intracavernous pressure to mean arterial pressure, were significantly improved compared to the unmodified BMMSCs, and PBS groups, though still lower than those in the normal control group. Additionally, the levels of capillary density, as well as Bcl-2 mRNA and protein expression, in the Bcl-2-BMSCs group were comparable to those in the normal control group and significantly higher than those in other treatment groups. While the study offered valuable insights into the potential of combining Bcl-2 with BMMSCs for treating diabetes mellitus-induced erectile dysfunction, further

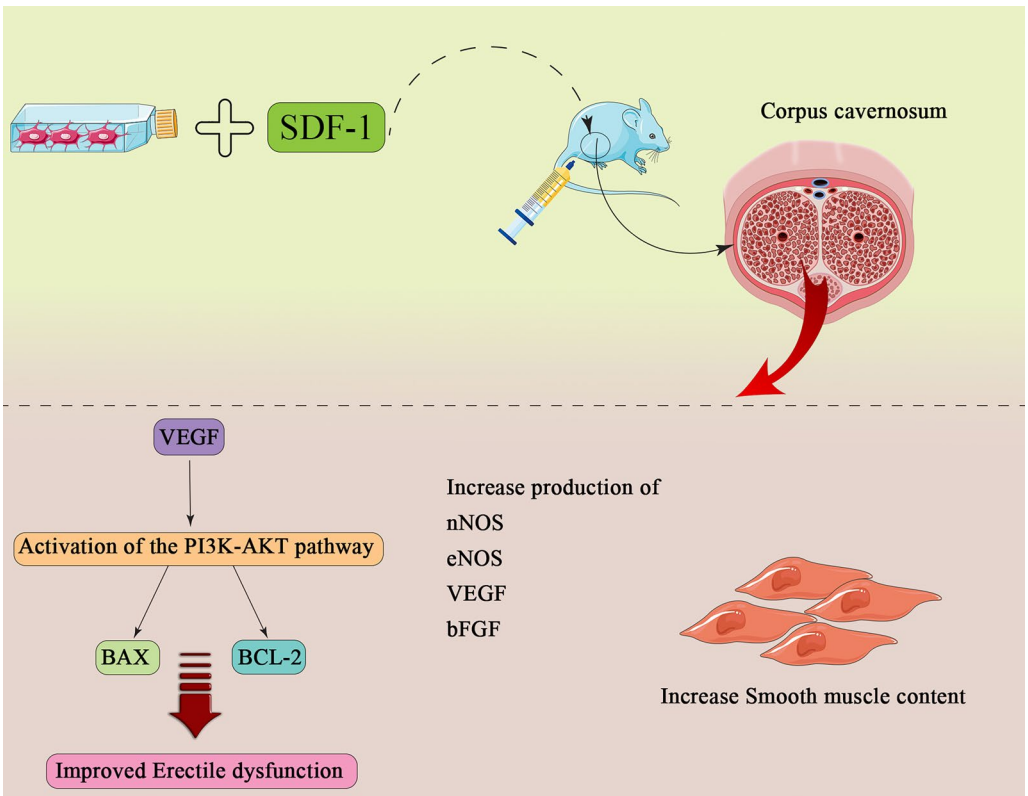


Fig. 2 Therapeutic effects of SDF-1-engineered MSCs on erectile dysfunction in a diabetic rat model. SDF-1-engineered MSCs improved erectile function by increasing smooth muscle content and upregulating nNOS, eNOS, VEGF, and bFGF in the corpus cavernosum. VEGF-induced activation of the PI3K-AKT pathway enhanced cell survival by increasing Bcl-2 and reducing Bax levels, promoting the viability and functionality of transplanted MSCs

research is necessary to investigate the impact of Bcl-2 gene-modified BMMSCs on the restoration of complex cellular functions, including migration, homing, and tissue repair, especially given the significant genomic instability associated with these modifications.

MSC-EVs in erectile dysfunction

MSCs exhibit secretory properties that contribute to their anti-inflammatory, antifibrotic, and immunosuppressive effects. Recent evidence suggests that these therapeutic effects may be largely mediated by EVs released from sources such as BM, AD, UC, menstrual blood, and dental pulp [96–99]. Recent research indicated that EVs secreted by MSCs exhibit therapeutic effects comparable to those of the MSCs themselves. This similarity arises because many of the paracrine actions of MSCs are mediated through EVs. These EVs deliver functional molecules such as miRNAs, mRNAs, and proteins, which play a crucial role in the therapeutic outcomes of MSCs in various diseases [100–103]. Research has demonstrated that EVs derived from MSCs show therapeutic efficacy in various animal models, including those for stroke [104], hind-limb ischemia [105], cutaneous wounds [106], and kidney diseases [107].

To the best of our knowledge, the potential use of MSC-derived EVs in treating cavernous nerve injury-induced erectile dysfunction remains largely unexplored. In this context, Ouyang et al. investigated the therapeutic efficacy of intracavernosal MSC-EVs injection for nerve injury-induced erectile dysfunction. Their study was based on the hypothesis that MSC-EVs may mitigate erectile dysfunction by reducing apoptosis in corpus cavernosum smooth muscle cells [108]. MSC-EVs treatment enhanced smooth muscle content, eNOS, and the smooth muscle-to-collagen ratio in the corpus cavernosum. It also increased corpus cavernosum smooth muscle cell viability and reduced caspase-3 expression both in vivo and in vitro. These findings suggested that MSC-EVs, isolated via ultracentrifugation, effectively ameliorated cavernous nerve injury-induced erectile dysfunction by inhibiting corpus cavernosum smooth muscle cell apoptosis. This cell-free approach offered comparable efficacy to MSC therapy, presenting a promising alternative for treating cavernous nerve injury-induced erectile dysfunction. In another study by Liu et al. [109], the therapeutic mechanism of MSC-EVs was investigated in a rat model of internal iliac artery injury-induced ED. MSC-EVs significantly enhanced erectile function following intracavernous injection. They promoted cavernous sinus endothelial formation, reduced oxidative stress damage, and increased NOS and smooth muscle content in the corpus cavernosum. With similar efficacy to MSC therapy and distinct advantages, MSC-EVs demonstrated potential as a promising treatment for restoring erectile function following arterial injury. Li et al. [110] demonstrated that MSC-EVs therapy restored the histological structure of the corpus cavernosum by enhancing smooth muscle-to-collagen ratios. Exosomal miR-296-5p and miR-337-3p target and inhibit PTEN, thereby modulating the PI3K/AKT signaling pathway. Additionally, exosomes derived from MSCs reduce apoptosis in corpus cavernosum smooth muscle cells. These findings indicated that MSC-exosomes improved age-related erectile dysfunction by delivering miR-296-5p and miR-337-3p to regulate the PTEN/PI3K/AKT pathway, highlighting their therapeutic potential for age-related erectile dysfunction treatment. A limitation of their study was that they only identified the differential expression of miR-296-5p and miR-337-3p between normal and aged rats. To better understand the mechanisms of age-related erectile dysfunction and uncover potential therapeutic targets, a more detailed miRNA expression profiling in the penile tissue of both normal and aged rats is needed.

Diabetic erectile dysfunction is associated with increased apoptosis and impaired smooth muscle proliferation in the corpus cavernosum, partially attributed to dysregulated molecular pathways. Recent studies have highlighted the role of programmed cell death protein 4 (PDCD4) and miR-21-5p in this process [111]. Elevated PDCD4 expression in diabetic erectile dysfunction rat cavernous tissue correlates with cellular apoptosis, while miR-21-5p, delivered via MSC-derived EVs, has been shown to inhibit PDCD4 activity. Suppression of PDCD4 led to upregulation of Bax and downregulation of BCL-2 and PCNA, which collectively contribute to enhanced corpus cavernosum smooth muscle cell proliferation and reduced apoptosis under high-glucose conditions (Fig. 3). Moreover, treatments targeting PDCD4 or leveraging miR-21-5p-enriched MSC-exosomes significantly restored smooth muscle density and erectile function in diabetic erectile dysfunction models, suggesting potential therapeutic avenues for diabetic erectile dysfunction management [112]. Another study investigated the effect of exosomes derived from miR-301a-3p overexpressing ADMSCs in rats with erectile dysfunction [113]. Their findings demonstrated that treatment with miR-301a-3p-enriched exosomes significantly improved erectile function in rats and corpus cavernosum smooth muscle cells by promoting autophagy and reducing apoptosis. The therapy also restored the expression of α-SMA, a key marker of smooth muscle integrity, in both experimental models. Bioinformatics analyses suggested that PTEN and TLR4 are potential targets of miR-301a-3p, providing insight into the molecular mechanisms underlying its therapeutic effects.

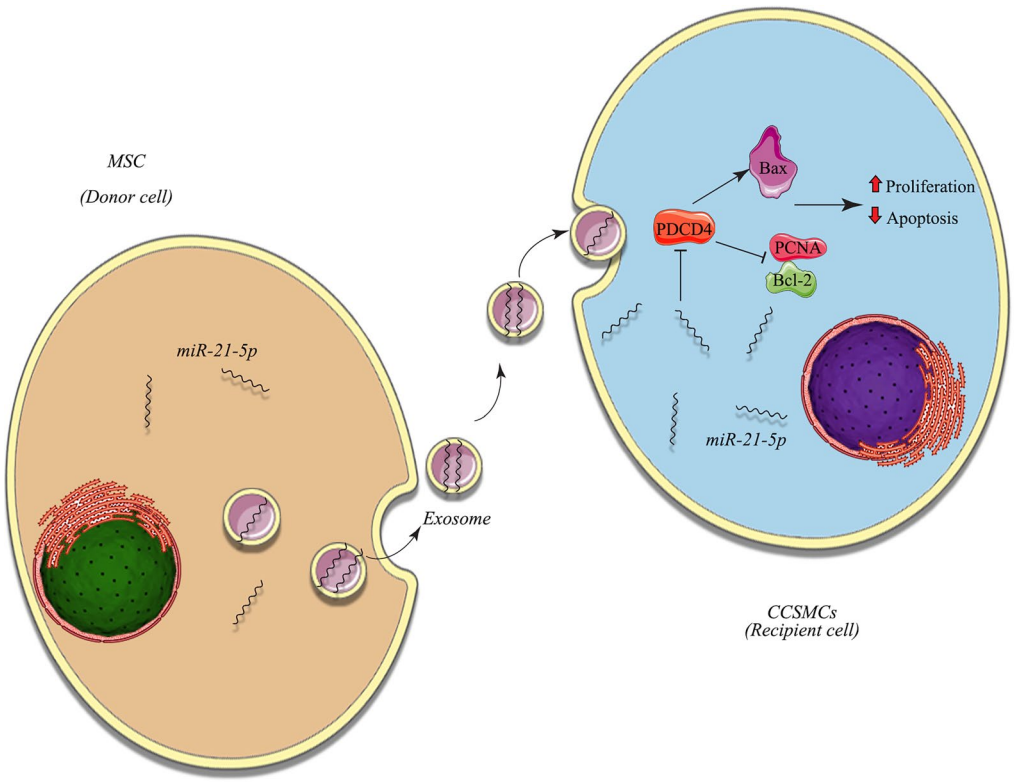


Fig. 3 Role of PDCD4 and miR-21-5p in regulating corpus cavernosum smooth muscle cell apoptosis and proliferation in diabetic erectile dysfunction. Elevated PDCD4 expression in diabetic rat cavernous tissue promotes apoptosis, while miR-21-5p, delivered via MSC-derived extracellular vesicles (EVs), inhibits PDCD4 activity. Suppression of PDCD4 results in increased Bax expression and decreased BCL-2 and PCNA levels, enhancing smooth muscle cell proliferation and reducing apoptosis under high-glucose conditions

Clinical application of MSCs in erectile dysfunction

Growing data has demonstrated the therapeutic benefits of MSCs in the clinical management of erectile dysfunction)Table 1(. For instance, You et al. [114] conducted an open-label phase 1 clinical trial involving the infusion of 3×10^7 BMMSCs into 10 patients with erectile dysfunction (five with post-prostatectomy erectile dysfunction and five with diabetic mellitus-induced erectile dysfunction). The trial demonstrated the safety and potential efficacy of autologous BMMSC therapy in treating erectile dysfunction. However, these findings require validation through a phase 2 clinical trial to confirm their therapeutic promise. The small sample size and lack of a control group are significant limitations that affect the reliability and generalizability of the results, underscoring the need for larger-scale, randomized studies. Furthermore, only a single, relatively low dose of BMMSCs was administered, a decision informed by data from an earlier preclinical study. These factors may restrict the applicability of the findings to larger clinical populations. In another study conducted by Mirzaei et al. [115], 20 diabetic patients with erectile dysfunction were randomized to receive $5–6\times10^7$ autologous MSCs derived from oral mucosa. Erectile function in the intervention group showed noticeable improvement over time, reflected in progressively higher International Index of Erectile Function (IIEF5) scores at three and six months post-injection. Compared to the control group, changes in IIEF5 scores in the intervention group were significantly greater over the six-month period. Although penile vascular parameters like peak systolic velocity (PSV) and resistance index (RI) did not differ significantly between groups, the intervention group exhibited positive trends in these measures. The relatively short follow-up period and small sample size limit the ability to draw conclusions about long-term efficacy. Additionally, patient hesitance due to discomfort highlights the need for refining the administration method to improve patient acceptance.

In a recent pilot study, 10 diabetic men suffering from erectile dysfunction were administrated by autologous BMMSCs and followed them for 24 weeks with Doppler parameters and the IIEF5. Out of ten participants, four achieved erections suitable for satisfactory intercourse, while two others required 100 mg sildenafil to

Table 1 Therapeutic benefits of mesenchymal stem cells (MSCs) in the clinical management of erectile dysfunction

Type of disease	Patient number	Cell origin	Injection method	Dosage	Follow-up period	Side effects	Outcomes	Reference
DIED	20	BMMSCs	IC	$5–6\times10^7$ cells	6 months	No severe effects	Improved sexual function, as well as PSV and RI	[115]
DIED	10	BMMSCs	IC	NM	6 months	No severe effects	Improved EDV and PSV	[118]
DIED	8	ADMSCs + PL	IC	$38.9\pm14.4\times10^6$ cells 2.2 ± 0.3 mL	3 months	No severe effects	Improved penile triplex and increased morning erections	[117]
DIED	22	WJ-MSCs	IC	0.25×10^5 cells	12 months	No severe effects	Significant improvements in IIEF-5, EHS, and PSV	[116]
DIED	4	BMMSCs	IC	0.25×10^5 cells	12 months	No severe effects	There was significant improvement of Erectile Function, Sexual Desire, Intercourse Satisfaction, and Overall Satisfaction	[119]
CAD	36	BMMSCs	Transendocardial	20×10^7 cells	12 months	No severe effects	High cell dose provided the best response	[120]
DIED post-prostatectomy ED	5 5	BMMSCs	IC	3×10^7 cells	12 months	No severe effects	Confirmed the safety and potential efficacy of MSCs therapy in patients with ED	[114]

DIED, diabetes-induced erectile dysfunction; IC, Intracavernosal; CAD, Cardiomyopathy

attain sufficient penile rigidity. Notably, PSV significantly improved in four patients, and variations in end-diastolic velocity (EDV) markedly increased in two individuals with venogenic insufficiency during follow-up. No severe adverse effects related to the transplant procedure were reported.

In a phase I/II clinical trial conducted by Al Demour et al. [116], 22 patients with diabetes-induced erectile dysfunction received intracavernous injections of allogeneic WJ-MSCs. The treatment involved two doses, administered 30 days apart, with each dose consisting of 2×10^7 cells in 4 mL. The study reported no serious adverse effects among participants. Significant improvements were observed in the IIEF-5, Erection Hardness Score (EHS), PSV at baseline, and 20-min PSV throughout the follow-up period compared to baseline measurements. A decline in positive effects observed between 6 and 12 months of follow-up suggests that the improvement in erectile function might be temporary. The open-label design and absence of a control group in this study might have led to bias, and the brief follow-up duration hinders a comprehensive assessment of the long-term therapeutic efficacy. Future research should aim to incorporate blinding, larger groups of patients, and extended follow-up durations to enhance the robustness of the findings. In another study, the use of autologous ADMSCs combined with platelet lysate (PL) was evaluated in patients with erectile dysfunction linked to conditions such as diabetes mellitus, hypertension, hypercholesterolemia, and Peyronie's disease. Eight patients were divided into two groups: Group A received ADMSCs resuspended in PL, while Group B received PL alone. Both treatments significantly improved erectile function, as reflected by increased IIEF-5 scores at one and three months post-treatment, though no significant differences were observed between the two groups. Enhancements in penile triplex parameters and morning erections were noted in all patients. No severe adverse effects occurred except for mild, tolerable injection-site pain. These findings highlight the potential of ADMSCs and

PL, individually or in combination, as promising and safe alternatives to conventional ED therapies [117].

In summary, while clinical studies indicate that MSC therapy shows potential for treating erectile dysfunction, there are several drawbacks, including limited sample sizes, absence of control groups, and brief follow-up periods. These issues impede the capacity to generalize the results and evaluate the long-term safety and effectiveness of MSC-based treatments. Future investigations should focus on performing large-scale, randomized controlled trials with longer follow-up times to fill these gaps. Moreover, standardized protocols for MSC preparation, dosing, and administration are essential to improve consistency and therapeutic results.

Challenges in the management of erectile dysfunction

Erectile dysfunction is a common condition that affects a large number of men worldwide, with serious impacts on their overall quality of life and mental health. Despite the availability of treatments like PDE5i, these drugs don't always work for everyone, particularly those with other health conditions such as diabetes, hypertension, or heart disease or for men who have had prostate surgery. One of the biggest challenges in treating erectile dysfunction is that it has many different causes—ranging from problems with blood vessels and nerves to hormonal imbalances and emotional factors—so finding a one-size-fits-all solution is difficult.

In recent years, new treatment options have been explored, especially in the field of regenerative medicine. Approaches like stem cell therapy, platelet-rich plasma (PRP) injections, and exosome treatments aim to go beyond just alleviating the symptoms of erectile dysfunction, instead focusing on addressing the root causes. Research suggests that these therapies can improve erectile function by promoting blood vessel growth, reducing cell death, and encouraging the regeneration of smooth muscle cells. For example, MSC-derived exosomes have been shown to help repair tissue and reduce inflammation, potentially offering a more targeted solution. However, these approaches face several challenges in clinical practice.

One major issue is that the outcomes of regenerative therapies can vary widely from patient to patient. Additionally, there is still no standardized approach for preparing and administering these treatments, and the benefits may not last long enough to make them practical for long-term use. Ethical concerns about stem cell research and the need for more rigorous clinical trials to prove the safety and effectiveness of these treatments add another layer of complexity. Patients' individual health profiles—such as the underlying cause of their erectile dysfunction and any other health conditions they may have—also play a significant role in how well these treatments work, highlighting the need for personalized care plans.

Beyond regenerative therapies, there is also growing interest in combining different treatment strategies. This could include a mix of medications, lifestyle changes, psychological counseling, and emerging therapies like low-intensity shockwave therapy. Although these options show potential, they also reflect the challenge of addressing erectile dysfunction from multiple angles and require cooperation between different medical specialties.

In conclusion, while there is progress in erectile dysfunction treatment, managing this condition remains difficult due to its complex causes and the limitations of current therapies. Regenerative medicine offers promising new avenues, but there are still hurdles to overcome, such as ensuring consistent results, refining techniques, and ensuring treatments are both safe and effective. Continued research into personalized treatment strategies and new technologies will be key to making more lasting improvements in erectile dysfunction care.

Conclusion

Research into MSC-derived exosomes and stem cell therapies for erectile dysfunction has shown considerable promise, with numerous studies highlighting their potential to enhance erectile function by fostering tissue repair, reducing inflammation, and regenerating smooth muscle cells. The paracrine effects of MSCs, including the release of exosomes, have yielded positive therapeutic outcomes in various erectile dysfunction models, such as those induced by nerve injury, diabetes, and aging. Clinical trials further support the safety and efficacy of these therapies, demonstrating notable improvements in erectile function and key clinical indicators like the IIEF-5 and penile vascular parameters.

However, several challenges persist in translating these therapies into widespread clinical practice. The complex and diverse nature of erectile dysfunction, along with the variability in patient responses, underscores the need for standardized protocols for MSC and exosome administration. While early-phase clinical trials show promise, larger, more comprehensive studies are necessary to confirm the long-term effectiveness and consistency of these treatments.

Ethical concerns surrounding stem cell research and the need for more rigorous, large-scale trials add further complexity to the path toward broader clinical implementation. To optimize patient outcomes, personalized treatment strategies tailored to individual health profiles and the underlying causes of erectile dysfunction will be critical.

In conclusion, MSC-derived exosome therapy represents a groundbreaking approach to the treatment of erectile dysfunction, offering a potential alternative to traditional therapies. Continued research and refinement of these techniques are essential for overcoming current challenges and achieving consistent, durable benefits for patients, ultimately paving the way for a transformative shift in erectile dysfunction treatment.

Abbreviations

AD	Adipose tissue
ABs	Apoptotic bodies
BM	Bone marrow
bFGF	Basic fibroblast growth factor
CM	Conditioned medium
EVs	Extracellular vesicles
ECM	Extracellular matrix
EPCs	Endothelial progenitor cells
EDV	End-diastolic velocity
EHS	Erection hardness score
MSCs	Mesenchymal stromal/stem cells
MVs	Microvesicles
MVBs	Multivesicular bodies
mtROS	Mitochondrial reactive oxygen species
MPGs	Major pelvic ganglia
nNOS	Nitric oxide synthase
NGF	Nerve growth factor
NRG1	Neuregulin-1
IGF-1	Insulin-like growth factor-1
ISCT	International Society for Cellular Therapy
ICP	Intracavernous pressure
LESWT	Low-energy shock-wave therapy
hWJ-MSCs	Human Wharton's jelly MSCs
Keap1	Kelch-like ECH-associated protein 1
PDE5i	Phosphodiesterase type 5 inhibitors
PRDX2	Peroxiredoxin 2
PDCD4	Programmed cell death protein 4
PL	Platelet lysate
PSV	Peak systolic velocity
SDF-1	Stromal cell-derived factor-1
RI	Resistance index
VROS	Reactive oxygen species
SOD	Superoxide dismutase
UC	Umbilical cord
VEGF	Vascular endothelial growth factor

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