ISSN 1948-9358 (online)

# World Journal of *Diabetes*

*World J Diabetes* 2021 December 15; 12(12): 1969-2129

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 12 Number 12 December 15, 2021

*World Journal of Diabetes*

**Monthly Volume 12 Number 12 December 15, 2021**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Caterina Conte, MD, PhD, Associate Professor, Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome 0166, Italy. caterina.conte@uniroma5.it

## AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJD* mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

## INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJD* as 3.763; IF without journal self cites: 3.684; 5-year IF: 7.348; Journal Citation Indicator: 0.64□Ranking: 80 among 145 journals in endocrinology and metabolism; and Quartile category: Q3.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Diabetes*

**ISSN**
ISSN 1948-9358 (online)

**LAUNCH DATE**
June 15, 2010

**FREQUENCY**
Monthly



**PUBLICATION DATE**
December 15, 2021

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

*World J Diabetes* 2021 December 15; 12(12): 2000-2010

DOI: 10.4239/wjd.v12.i12.2000

ISSN 1948-9358 (online)

*MINIREVIEWS*

# Progress and prospect of stem cell therapy for diabetic erectile dysfunction

Dao-Sheng Luo, Yan-Qing Li, Zhi-Quan Deng, Gui-Hua Liu

**ORCID number:** Dao-Sheng Luo 0000-0003-0427-0668; Yan-Qing Li 0000-0003-3222-5610; Zhi-Quan Deng 0000-0002-3946-5126; Gui-Hua Liu 0000-0003-1811-8763.

**Author contributions:** Liu GH and Luo DS designed the research study; Luo DS and Li YQ performed the literature retrieval and analysis; Li YQ and Deng ZQ wrote the manuscript; All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** The authors declare that there are no conflicts of interest associated with this manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81971759.

**Country/Territory of origin:** China

**Specialty type:** Andrology

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**Dao-Sheng Luo, Zhi-Quan Deng,** Department of Urology, Dongguan People's Hospital, Dongguan 523000, Guangdong Province, China

**Yan-Qing Li, Gui-Hua Liu,** Reproductive Centre, Sun Yat-Sen University, The Sixth Affiliated Hospital, Guangzhou 510000, Guangdong Province, China

**Corresponding author:** Guihua Liu, MD, PhD, Associate Chief Physician, Associate Research Scientist, Reproductive Centre, Sun Yat-Sen University, The Sixth Affiliated Hospital, No. 26 Yuancuner Rd., Tianhe District, Guangzhou 510000, Guangdong Province, China. liuguihua@mail.sysu.edu.cn

## Abstract

Diabetic erectile dysfunction (DED) is a common complication of diabetes mellitus, significantly impairing the quality of life of patients. The conventional clinical treatment still has limitations. Stem cells (SCs), as a type of cells with multidirectional or directional differentiation capability and sustainable self-renewal potential, are widely used in regenerative medicine and tissue engineering. With the continuous update of regenerative medicine theory and the success of animal experiments, SCs as a treatment for male erectile dysfunction, especially DED, have attracted widespread attention because of curable possibility. This review focus on the current progress in the clinical application of SC treatment for DED. Moreover, we summarize the development prospects of SCs in the field of DMED therapy.

**Key Words:** Stem cell; Diabetic erectile dysfunction; Extracellular vesicles; Gene editing



**Core Tip:** Diabetic erectile dysfunction (DED) is a common complication of diabetes. Conventional clinical treatments like phosphodiesterase-5 inhibitors, intracavernosal vasoactive drug injection, negative pressure suction device, and low-intensity shock wave therapy are the conventional methods of clinical treatment. However, none of the above therapies has the potential of curing. Stem cell therapy is currently the only possible cure for DED and can avoid the potential complications of conventional therapies. Here we discuss the current role and progress of stem cells in the treatment

**Received:** February 6, 2021
**Peer-review started:** February 7, 2021
**First decision:** March 8, 2021
**Revised:** March 18, 2021
**Accepted:** October 31, 2021
**Article in press:** November 3, 2021
**Published online:** December 15, 2021

**P-Reviewer:** Yang Q
**S-Editor:** Liu M
**L-Editor:** Wang TQ
**P-Editor:** Liu M

of DED.

**Citation:** Luo DS, Li YQ, Deng ZQ, Liu GH. Progress and prospect of stem cell therapy for diabetic erectile dysfunction. *World J Diabetes* 2021; 12(12): 2000-2010
**URL:** https://www.wjgnet.com/1948-9358/full/v12/i12/2000.htm
**DOI:** https://dx.doi.org/10.4239/wjd.v12.i12.2000

## INTRODUCTION

Diabetes mellitus (DM) is a chronic, non-communicable disease caused by genetic, environmental, and other factors. Over the past three decades, the number of people with DM has more than doubled globally, making it one of the most important public health challenges worldwide[1]. Erectile dysfunction, defined as the inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse [2], is a major complication of DM[3]. Diabetes is considered the main risk factor for the development of erectile dysfunction, and since the 1970s, the association between diabetes and the development of erectile dysfunction has been documented both in animal models and humans[4]. Increasing attention focuses on erectile dysfunction in men with diabetes due to its multifactorial pathophysiology and the concurrence of the same components as vasculopathy, neuropathy, and depression[5]. Although oral phosphodiesterase-5 inhibitors (PDE5Is) represent as a successful first-line therapy, a considerable proportion of men do not respond to oral PDE5Is[6-8]. Other conventional therapeutics for ED consist of oral medications, intracavernosal injections, vacuum erection devices, and penile implants. However, due to the lack of high quality evidence of efficacy and safety, poor patient compliance, and poor treatment outcomes, the above treatment regimens are still controversial in clinical application[9-13]. Recent 20 years have witnessed the progress of stem cell therapy (SCT), and it is expected to be an alternative option in the treatment of diabetic erectile dysfunctions (DED) and replace the current conventional treatment options.

## STEM CELL THERAPEUTIC POTENTIAL AND CLASSIFICATION

The term ‘stem cells’ encompasses various cells with self-renewal and differentiation abilities, and many of them can potentially be used therapeutically[14,15]. In addition to differentiation into mature tissue cells, stem cells can also play a therapeutic role due to their chemotaxis, anti-inflammatory, regenerative, angiogenic, and anti-apoptotic properties[16-21]. A large number of regenerative medicine studies have proved the therapeutic potential of stem cells[22].

There are two major types of stem cells, embryonic stem cells (ESCs) and adult stem cells (ASCs)[14]. ESCs are derived from the inner cell mass of preimplantation embryos. Limited by biological and medical ethics, the clinical application of ESCs in the treatment of ED is restricted[23]. ASCs are ethical and easier to obtain from the host. Therefore, ASCs derived from patients themselves have been favored by researchers in recent years[24-31]. At present, many preclinical studies have used various types of ASCs to confirm the conclusion of improving erectile function, including bone marrow-derived mesenchymal stem cells (BMSCs)[32], adipose-derived stem cells (ADSCs)[33], neuro-derived stem cells[34], mesenchymal stem cell (MSCs)[35] , and urine-derived stem cells (USCs)[36,37]. They are characterized by the narrowest differentiation capabilities and a special property of dividing repeatedly, making them a promising candidate for therapeutic use in regenerative medicine.

In 2006, Takahashi and Yamanaka[38] reported a method to reprogram multipotent ASCs to the pluripotent state. Retrovirus-mediated transduction of mouse fibroblasts with four transcription factors (Oct-3/4, Sox2, KLF4, and c-Myc) could induce the fibroblasts to become pluripotent. This new form of stem cells is named induced pluripotent stem cells (iPSCs)[39]. One year later, the experiment also succeeded with human cells[40]. iPSCs opened a new field in stem cell research, because they can proliferate indefinitely and differentiate into any kind of cell with unlimited sources. iPSCs bypass the need for embryos in SCT, because they are obtained from the host patient’s own cells, and they are autologous and no longer generate any risk of

immune rejection[41,42] (Table 1).

## STEM CELL THERAPY IN DIABETIC ERECTILE DYSFUNCTION MODELS

Stem cell-based therapies have been investigated in the field of DED. The overall aim is to repair the underlying corpus cavernosum cellular damage. Yang *et al*[43] injected ADSCs and endothelial progenitor cells (EPC) alone or in combination in DMED rat models and found that on the 28$^{th}$ day after injection, the mean arterial pressure (MAP) ratio were significantly higher in the ADSC group, EPC group, and ADSC combined with EPC group than in the DED group, and in the ADSC combined with EPC group than in the DED group, ADSC group, and EPC group ($P < 0.05$). It is revealed that both ADSCs and EPCS can improve erectile function, and the combined transplantation of ADSCs and EPC can synergistically improve the endothelial function in DMED rats. The therapeutic effect is better than the treatment with ADSCs or EPCs alone. Zhang *et al*[44] explored the therapeutic mechanism of USCs, using advanced glycation end products to treat rat cavernous endothelial cells to simulate a diabetic environment. Then, the two cells were co-cultured to evaluate the protective effect of USCs *in vitro*. Finally, they concluded that autophagy dysfunction is related to cavernous endothelial function and erectile dysfunction in DMED rats. In addition, USCs can up-regulate the autophagy activity of sponge endothelial cells, which improves endothelial sponge dysfunction and is ultimately expected to improve erectile dysfunction caused by diabetes. These stem cell-based preclinical studies have emphasized the improvement of the erectile function of DED animals after stem cell treatment and explained the underlying mechanism.

Some researchers also explored the combination of stem cells with conventional therapy. Liu *et al*[45] conducted related studies and used hepatocyte growth factor (HGF) combined with ADSCs to treat DMED rat models. One month later, treatment with ADSCs alone can significantly improve the erectile function of diabetic rats. However, the combined application with HGF has a more significant effect, making the erectile function even close to the normal level. It shows that HGF can significantly enhance the beneficial effects of ADSCs on the erectile function of diabetic rats, and its mechanism may be closely related to the down-regulation of the TGF-β1-Smad signaling pathway. Shan *et al*[46] combined BMSCs and low energy shock wave (LESWT) to treat a DMED rat model. On days 1, 3, and 28 after BMSC transplantation, they observed the number of surviving BMSCs in the cavernous body. The result showed that combined application of LESWT and BMSC transplantation maintained more BMSCs in cavernous body and improved the erectile function of diabetic rats more effectively than LESWT or BMSC transplantation alone. This may promote the expression of stromal cell-derived factor-1 in the diabetic cavernous tissue, thus promoting angiogenesis. In another study, Jung *et al*[47] used an oxygen-releasing hollow microparticle (HP) system with human BMSC to attempt to overcome certain limitations of SCT, including insufficient nutrient and oxygen supplies for transplanted stem cells. The results demonstrated that a stem cell/oxygen-releasing HP hybrid system could further improve erectile function, cyclic guanosine monophosphate level, and nitric oxide synthase (NOS) level in a bilateral cavernous nerve injury rat model through prolonged stem cell survival. Their data suggest that a stem cell/oxygen-releasing HP system is a promising clinical treatment option for postprostatectomy erectile dysfunction. Furthermore, this system may be relevant in different disease therapies and regenerative medicine.

Next-generation stem cells may serve as therapeutic agents by overexpressing neurotrophic factors, chemokines, anti-inflammatory molecules, angiogenic factors, and other molecules that aid in recovery and endogenous repair of tissues[48]. Modified stem cells may repair the damaged signaling pathway in DED that causes endothelial dysfunction, confirmed by various studies. We have prepared ADSCs expressing large amounts of vascular endothelial growth factor (VEGF) through virus transfection[49], and found that these ADSCs could stimulate endothelial function, increase the content of smooth muscle and pericytes, and significantly improve the erectile function of DED rats. Kizub *et al*[50] also conducted similar experiments in MSCs, and MSCs expressing VEGF also showed the same advantages. In addition, ADSC injection combined with insulin therapy can produce better therapeutic effects in a DMED rat model[51]. The above experiments show that stem cell injection can help restore the erection and other physiological functions of the penis.

The use of stem cell-derived extracellular vesicles (EVs) avoids the risks of any undesired stem cell growth or potential for tumor-promoting effects, which has been

**Table 1 Characteristics of the articles published**

| Ref. | Treatment factor | Method/transfer/period | Evidence | Outcome |
|---|---|---|---|---|
| [42] | Rat<br><br>ADSCs/EPCs/combined ADSCs and EPCs | Injection with ADSCs ($1 \times 10^6$), EPCs ($1 \times 10^6$), and ADSCs/EPCs ($0.5 \times 10^6/0.5 \times 10^6$) | ADSC/EPC group displayed more significantly enhanced ICP and ICP/MAP than the DED or ADSC or EPC group ($P < 0.05$). (After 28 d) | Combined transplantation of ADSCs and EPCs has a synergic effect in repairing the endothelial function of DED rats |
| [43] | Human USCs | Coculture of USCs and rat corpus (CCECs) treated with AGEs/injection with USCs ($1 \times 10^6$) in rat DED model | USCs protected CCECs from AGE-induced autophagic dysfunction and cellular damage/DED rats showed lower ratio of ICP/MAP, reduced expression of endothelial markers, and fewer autophagic vacuoles in the cavernosal endothelium | Intracavernous injection of USCs up-regulates autophagic activity in the cavernosal endothelium |
| [44] | Combined HGF and ADSCs | Injection with ADSCs alone or combined with HGF | Significant down-regulation of TGFβ1-Smad signaling | HGF enhance the beneficial effects of ADSCs on DED through down-regulation of the TGFb1-Smad signaling pathway |
| [45] | Combined BMSCs and LESWT | 1/3 d after BMSC transplantation, the number of surviving BMSCs in the cavernous body was counted | LESWT favored the survival of transplanted BMSCs in the cavernous body, increased stromal cell-derived factor-1, and enhanced angiogenesis | Combined LESWT and BMSC improve the erectile function of DED rats more effectively than either alone |
| [46] | HP and human BMSCs | hBMSC ($1 \times 10^6$ cells/mL) seeded on oxygen-saturated HPs | cGMP and NOS levels rose through prolonged stem cell survival | Stem cell/oxygen-releasing HP hybrid system could further improve erectile function |
| [48] | ADSCs expressing VEGF | ADSCs expressing large amounts of VEGF through virus transfection | VEGF-ADSCs stimulated endothelial function, and increased the content of smooth muscle and pericytes | VEGF-ADSCs improve erectile function |
| [57] | ADSC EVs | ADSC EVs through ultracentrifugation and treatment of DED rat model through ICI | ADSC-derived EXOs and ADSCs increased the ratio of intracavernous pressure | ADSC-derived EXOs and ADSCs are able to rescue corpus cavernosum endothelial and smooth muscle cells by inhibiting apoptosis |
| | USC EVs | USC EVs through ultracentrifugation and treatment of DED rat model through ICI | USC-EVS enhanced the expression of endothelial cell markers in DED rats, reduced collagen deposition, and improved neurogenic erectile response through pro-angiogenic miRNAs | USC-EV transplantation can ameliorate DED in rats *via* mechanisms that may involve the delivery of proangiogenic miRNAs |

ADSCs: Adipose tissue-derived stem cells; EPCs: Endothelial progenitor cells; ICP: Intracavernous pressure; MAP: Mean arterial pressure; DED: Diabetic erectile dysfunction; CCECs: Cavernosal vascular endothelial cells; AGEs: Glycation end products; HGF: Hepatocyte growth factor; BMSCs: Bone marrow mesenchymal stem cells; LESWT: Low energy shock wave; HPs: Oxygen-releasing hollow microparticles; EVs: Extracellular vesicles; USCs: Urine derived stem cells.

noted for MSCs in certain situations[52]. At present, stem cells are widely used as biomaterials for the regeneration of tissue defects. The treatment mechanism is based on the differentiation into specific target cells after implantation and the paracrine release effect of EVs[53,54]. EVs secreted by stem cells are believed to play a major role in the treatment of DED. The paracrine release effect of EVs means that the exosomes after injection can repair damaged tissues by delivering cytoprotective molecules, anti-inflammatory molecules, and anti-apoptotic molecules. Many studies support this view, proposing the direct use of stem cell EV therapy to restore the function of damaged organs and tissues and achieve the direction of cell-free SCT[55-57]. Chen *et al*[58] acquired ADSC EVs through ultracentrifugation and treated a DED rat model through intracavernous injection (ICI). The results show that, like ADSCs, exosomes derived from ADSCs can increase the number of sponge endothelial cells and smooth muscle cells by inhibiting cell apoptosis, thereby promoting the recovery of erectile function in type 2 diabetic rats. Ouyang *et al* used the same method to obtain the EVs of USCs[59]. Their results showed that USC-EVs enhance the expression of endothelial cell markers in DED rats, reduce collagen deposition, and improve neurogenic erectile response. The transport of pro-angiogenic microRNAs secreted by EVs may play an important role in endothelial repair. EVs secreted from engineered stem cells are considered an alternative cell-free next-generation approach for delivering vascular repair factors, anti-apoptosis agents, and other tissue-repairing agents.

## HUMAN CLINICAL TRIALS OF SCT

Although SCT has been proved effective in multiple animal ED models, there are only a few human clinical trials of SCT, thus we include clinical trials of other types of ED. Bahk *et al*[60] recruited seven patients with type 2 DED in the study, all of whom were insensitive to drug treatment for more than 6 mo and needed to wait for penile prosthesis implantation. The researchers injected 1.5 × 1.7 human umbilical cord blood cells into the cavernous body and recorded their International Erectile Function Index-5, Sexual Encounter Profile, Global Assessment Question, erectile diary, blood glucose diary, and medication dosage. The results showed that three of the six patients recovered the morning erection reaction after 1 mo, and it rose to five after 3 mo. At the 6 mo follow-up, two of the patients completed their sexual life and reached orgasm under the premise of oral PDE5i. After 9 mo, all five patients felt an increase in libido. During the entire follow-up process, two patients quit to implant a penile prosthesis, and four had recovered erectile function. And no side effect of SCT was reported. Levy *et al*[61] injected placental matrix-MSCs to treat patients with ED into eight patients with ED who had failed to take oral medications, and MSC treatment was followed at 6 wk, 3 mo, and 6 mo to assess peak systolic velocity (PSV), end diastolic velocity, stretched penile length, penile width, and erectile function status based on the International Index of Erectile Function questionnaire. The results showed that at 6 wk, two patients developed spontaneous and maintained erections; at 3 mo, one patient can erect spontaneously. The average PSV values of patients at 3 and 6 mo were significantly higher than those before treatment. However, the measured end-diastolic speed changes, extended penis length, penis width, and erectile function international index score were not statistically significant. In a phase 1 clinical trial[62], 12 patients who had ED after radical resection of prostate cancer (drug treatment failed) were given ICI of BMSCs four times, and the injection dose of BMSCs was increased gradually ($2 \times 10^7$, $2 \times 10^8$, $1 \times 10^9$, and $2 \times 10^9$). The results showed that 9 out of 12 patients exhibited significant improvement in erectile function under the premise of oral PDE5i. It was found that as the injection dose increased, the incidence of spontaneous erection increased, and the study did not report any serious adverse reactions after injection. In phase II clinical trial of the same study, six more patients were recruited, and the best dose ($1 \times 10^9$) of BMSCs determined in phase 1 was injected. The results showed that the sexual satisfaction scores of 18 patients in the IIEF-5 index and the erectile function scores were significantly improved compared to those before treatment. However, the six patients who participated in the second stage had lower erectile function scores than the 12 patients who participated in the first stage. In the first phase, no prostate cancer recurrence was detected[63]. In the phase I clinical trial conducted by Demour *et al*[64] in 2018, human BMSCs were used for the first time to treat DED. They included four patients with DED who had failed medical treatment and injected the BMSCs extracted from the patients into the penile sponge twice. The patients' tolerability was evaluated immediately after injection and 24 h later. The effectiveness was evaluated by IIEF-5 and EHS scores 1 year later, and safety was evaluated 2 years later. The results showed that all patients tolerated the operation well, and there was no obvious adverse reaction. After 12 mo of follow-up, the patients' IIEF-15, EHS, erectile function, libido, sexual satisfaction, and overall satisfaction scores were significantly improved compared to those before treatment. Haahr *et al*[65] discussed the effectiveness and safety of ADRCs in the treatment of patients with ED after RP. The researchers injected 21 patients' own ADSCs into the cavernous body at one time, followed them for 1 year, and evaluated and recorded adverse events, IIEF-5 score, and EHS score. The results showed that no serious adverse events occurred during the follow-up process, but eight cases had reversible adverse reactions related to liposuction, including three cases of redness and swelling in the penis and five cases of mild hematoma in the abdomen, all of which occurred within a short period of time after treatment and subsided without any sequelae. Eight of the 21 participants (38%) recovered sufficient erectile function during the 12-mo observation period. These eight patients had poor erection assistance effects before receiving stem cell treatment. After treatment, three men could complete sexual intercourse without erectile assistance. Six of all participants had erectile dysfunction before RP, and these six patients did not recover their erectile function after receiving SCT.

## DISSCUSSION

According to the current multiple preclinical studies and a small number of clinical studies for the treatment of organic ED with SCT, the effectiveness and safety of SCT are considerable, and it is also considered to be a very promising way to treat organic ED in the future. A meta-analysis included ten preclinical studies on SCT in ED rat models, with a total of 302 rats. The results showed that SCT improved erectile function in diabetic rats (standard mean difference = 4.03, 95% confidence interval: 3.22-4.84, $P < 0.001$)[66]. The contents of vascular smooth muscle and endothelial cells in the stem cell treatment group were significantly higher than those in the control group. The expression of endothelial NOS and neural NOS, smooth muscle/collagen ratio, and VEGF secretion were significantly increased. In addition, stem cell treatment can reduce apoptotic cells. Subpopulation analysis showed that modified stem cells were more effective than unmodified stem cells. These results suggested that SCT can significantly improve the erectile function of diabetic rats. Some specific modifications, especially the genetic modification of growth factors, can improve the effectiveness of SCT. SCT may become an effective strategy for the treatment of diabetic ED.

There are only nine clinical trials reporting the efficacy and safety of stem cell treatment in men with ED, and the trial sample size is less than 100 cases. Based on the results of each study, the overall penile hemodynamic and erectile function scores of patients are significantly improved. No major adverse reactions was observed.

After years of exploration in many preclinical trials, the current mechanism of SCT for organic ED has been clarified. There are two major hypotheses about SCT. First, SCT can repair and replace cavernous nerves. SC differentiate into cavernous nerve cells, smooth muscle cells, and endothelial cells[67]. Second, SCT provides penile tissue support through the paracrine effect of EVs, delivering proangiogenic, anti-inflammatory, anti-apoptotic, and anti-fibrotic properties[68]. Studies have shown that the release of paracrine repair cytokines is an endogenous mechanism independent of the differentiation of stem cells into different cell types[69].

Although SCT seems to have good prospects in the treatment of DED, there are still many unresolved challenges. First, there is still a lack of large-scale clinical studies to verify its effectiveness and safety. Although SCT has achieved great success in some animal experiments, due to the huge anatomy and physiology gap between animal DED model and human DED[70], it is difficult to clarify whether the successful results of animal experiments will still work in human DED due to the lack of high-quality and large-scale human trials of SCT. Most of existed clinical trials are phase I studies, with a small sample size and lack of blinding method, as well as ambiguous inclusion and exclusion criteria, and primary and secondary outcome indicators. The inclusion of negative studies makes these studies insufficient to provide convincing evidence.

Second, SCT may have safety issues. Although previous studies have not found serious complications after treatment, some studies reported that MSCs could penetrate into prostate cancer cells, including prostate tissue[71], and SCs may act as a tumor promoter to affect its occurrence and development[72].

Third, the cell source selection of SCT warrants further investigation. Existing studies have found that both autologous and foreign SCs can improve the erectile function in ED. As for the trade-off between the pros and cons of choosing autologous or allogeneic SCs, only one study has explored this issue, but it still does not directly compare the application of autologous cells and allogeneic cells[73]. It is believed that choosing autologous stem cells will bring obvious safety advantages and it is convenient to obtain materials because it can overcome the antigenic problem of allogeneic cell transplantation. However, recent studies have found that allogeneic ADSCs can induce a locally suppressed microenvironment by secreting intraoperative cytokines to regulate the function of natural killer cells and T cells, thereby avoiding allogeneic immune rejection[67]. Meanwhile, in another study on a rat model of acute myocardial infarction treated with SCs, it was found that allogeneic transplantation of MSCs only maintained their ability to overcome allogeneic immune rejection in a short period of time. As the treatment time prolonged, MSCs differentiated in myocardial tissue and lost their immune privilege status, thereby affecting the therapeutic effect [74]. Autologous stem cells are not suitable for all patients. For example, for elderly patients, the proliferation and differentiation ability of stem cells in the body decreases significantly as the body ages[75]. In addition, for cancer patients, the use of autologous stem cells for transplantation is prohibited[76].

Fourth, treatment methods have not yet been standardized. Multiple studies have demonstrated the presence of MSCs in the lung, immediately after injection[77-80]. However, the majority of cells are, however, cleared within the first days of treatment [81]. It is reported that less than 1% of stem cells injected intravenously in SCT actually

reached the target tissue, but the treatment effect was not affected[82]. Hence, there is a demand for retaining stem cells in the corpus cavernosum after ICI for ED therapy. ADSCs incubated with NanoShuttle were magnetic and maintained in the corpus cavernosum. This improved the adipose-derived SCT of ED in a CNI rat model[83]. Nevertheless, the cell type, the injection concentration, the course of treatment, and the evaluation endpoint of the treatment effect have not yet been determined.

Fifth, there are ethical issues. SCs constitute one of the most promising tools for regenerative medicine. Thus, it seems morally compelling to explore all the sources that might provide us with them. However, some of these sources, such as somatic cell nuclear transfer, embryo destruction, or even induced pluripotency obtained by reprogramming, have raised serious ethical issues[84]. For the use of cell, tissue, and stem-cell products in treating patients, the US Food and Drug Administration[85], the European Medicines Agency guidelines, and the International Society for Stem Cell Research have also developed or updated several specific guidelines for SCT with the help of stem cell experts from all around the world[86]. According to these guidelines, the most important topics of SCT related to ethical, legal, and social considerations of cell therapy include: (1) Manufacturing conditions and characterization of clinical-grade cells; (2) genetic material and confidential personal information; (3) informed consent; (4) genetic manipulation of the cells; and (5) intellectual property and patents, along with some other important issues[87].

## CONCLUSION

SCT for DED has broad development prospects. However, many problems need to be solved to achieve an effective and safe clinical treatment plan. In addition to the need to further clarify its specific mechanism of action, effectiveness, and safety, it is also necessary to clarify the optimal treatment plan to solve the immunogenicity and heterogeneity of SCT, and improve its high cost and low efficiency in application. In the future, more phase II and phase III clinical trials are needed to make full preparations for the transformation of SC treatment of ED from preclinical to clinical trials and translate into clinical applications.

## REFERENCES


1 **Chen L**, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. *Nat Rev Endocrinol* 2011; **8**: 228-236 [PMID: 22064493 DOI: 10.1038/nrendo.2011.183]

2 **Shamloul R**, Ghanem H. Erectile dysfunction. *Lancet* 2013; **381**: 153-165 [PMID: 23040455 DOI: 10.1016/S0140-6736(12)60520-0]

3 **Kouidrat Y**, Pizzol D, Cosco T, Thompson T, Carnaghi M, Bertoldo A, Solmi M, Stubbs B, Veronese N. High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. *Diabet Med* 2017; **34**: 1185-1192 [PMID: 28722225 DOI: 10.1111/dme.13403]

4 **Gur S**, Hellstrom WJG. Harnessing Stem Cell Potential for the Treatment of Erectile Function in Men with Diabetes Mellitus: From Preclinical/Clinical Perspectives to Penile Tissue Engineering. *Curr Stem Cell Res Ther* 2020; **15**: 308-320 [PMID: 31456525 DOI: 10.2174/1574888X14666190828142045]

5 **Lizza EF**, Rosen RC. Definition and classification of erectile dysfunction: report of the Nomenclature Committee of the International Society of Impotence Research. *Int J Impot Res* 1999; **11**: 141-143 [PMID: 10404282 DOI: 10.1038/sj.ijir.3900396]

6 **Hamidi Madani A**, Asadolahzade A, Mokhtari G, Shahrokhi Damavand R, Farzan A, Esmaeili S. Assessment of the efficacy of combination therapy with folic acid and tadalafil for the management of erectile dysfunction in men with type 2 diabetes mellitus. *J Sex Med* 2013; **10**: 1146-1150 [PMID: 23347176 DOI: 10.1111/jsm.12047]

7 **Ryu JK**, Suh JK, Burnett AL. Research in pharmacotherapy for erectile dysfunction. *Transl Androl Urol* 2017; **6**: 207-215 [PMID: 28540228 DOI: 10.21037/tau.2016.11.17]

8 **Kamenov ZA**. A comprehensive review of erectile dysfunction in men with diabetes. *Exp Clin Endocrinol Diabetes* 2015; **123**: 141-158 [PMID: 25502583 DOI: 10.1055/s-0034-1394383]

9 **McMahon CG**. Current diagnosis and management of erectile dysfunction. *Med J Aust* 2019; **210**: 469-476 [PMID: 31099420 DOI: 10.5694/mja2.50167]

10 **Mydlo JH**, Volpe MA, Macchia RJ. Initial results utilizing combination therapy for patients with a suboptimal response to either alprostadil or sildenafil monotherapy. *Eur Urol* 2000; **38**: 30-34 [PMID: 10859438 DOI: 10.1159/000020248]

11 **Hackett G**, Cole N, Saghir A, Jones P, Strange RC, Ramachandran S. Testosterone undecanoate

improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study. *BJU Int* 2016; **118**: 804-813 [PMID: 27124889 DOI: 10.1111/bju.13516]

12 **Seftel AD**. Re: Testosterone Therapy for Sexual Dysfunction in Men with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Urol* 2018; **199**: 1096 [PMID: 29677872 DOI: 10.1016/j.juro.2018.02.057]

13 **Meuleman EJ**. [Experiences with a vacuum apparatus in the treatment of erection disorders]. *Ned Tijdschr Geneeskd* 1993; **137**: 412-416 [PMID: 8446200]

14 **Zakrzewski W**, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther* 2019; **10**: 68 [PMID: 30808416 DOI: 10.1186/s13287-019-1165-5]

15 **Hass R**, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Commun Signal* 2011; **9**: 12 [PMID: 21569606 DOI: 10.1186/1478-811X-9-12]

16 **Steinberg GK**, Kondziolka D, Wechsler LR, Lunsford LD, Kim AS, Johnson JN, Bates D, Poggio G, Case C, McGrogan M, Yankee EW, Schwartz NE. Two-year safety and clinical outcomes in chronic ischemic stroke patients after implantation of modified bone marrow-derived mesenchymal stem cells (SB623): a phase 1/2a study. *J Neurosurg* 2018; 1-11 [PMID: 30497166 DOI: 10.3171/2018.5.JNS173147]

17 **Hess DC**, Wechsler LR, Clark WM, Savitz SI, Ford GA, Chiu D, Yavagal DR, Uchino K, Liebeskind DS, Auchus AP, Sen S, Sila CA, Vest JD, Mays RW. Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol* 2017; **16**: 360-368 [PMID: 28320635 DOI: 10.1016/S1474-4422(17)30046-7]

18 **Klein SM**, Behrstock S, McHugh J, Hoffmann K, Wallace K, Suzuki M, Aebischer P, Svendsen CN. GDNF delivery using human neural progenitor cells in a rat model of ALS. *Hum Gene Ther* 2005; **16**: 509-521 [PMID: 15871682 DOI: 10.1089/hum.2005.16.509]

19 **Akhtar AA**, Gowing G, Kobritz N, Savinoff SE, Garcia L, Saxon D, Cho N, Kim G, Tom CM, Park H, Lawless G, Shelley BC, Mattis VB, Breunig JJ, Svendsen CN. Inducible Expression of GDNF in Transplanted iPSC-Derived Neural Progenitor Cells. *Stem Cell Reports* 2018; **10**: 1696-1704 [PMID: 29706501 DOI: 10.1016/j.stemcr.2018.03.024]

20 **Liu YW**, Chen B, Yang X, Fugate JA, Kalucki FA, Futakuchi-Tsuchida A, Couture L, Vogel KW, Astley CA, Baldessari A, Ogle J, Don CW, Steinberg ZL, Seslar SP, Tuck SA, Tsuchida H, Naumova AV, Dupras SK, Lyu MS, Lee J, Hailey DW, Reinecke H, Pabon L, Fryer BH, MacLellan WR, Thies RS, Murry CE. Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nat Biotechnol* 2018; **36**: 597-605 [PMID: 29969440 DOI: 10.1038/nbt.4162]

21 **Hwang CW**, Johnston PV, Gerstenblith G, Weiss RG, Tomaselli GF, Bogdan VE, Panigrahi A, Leszczynska A, Xia Z. Stem cell impregnated nanofiber stent sleeve for on-stent production and intravascular delivery of paracrine factors. *Biomaterials* 2015; **52**: 318-326 [PMID: 25818438 DOI: 10.1016/j.biomaterials.2015.02.047]

22 **Terashvili M**, Bosnjak ZJ. Stem Cell Therapies in Cardiovascular Disease. *J Cardiothorac Vasc Anesth* 2019; **33**: 209-222 [PMID: 30029992 DOI: 10.1053/j.jvca.2018.04.048]

23 **Larijani B**, Esfahani EN, Amini P, Nikbin B, Alimoghaddam K, Amiri S, Malekzadeh R, Yazdi NM, Ghodsi M, Dowlati Y, Sahraian MA, Ghavamzadeh A. Stem cell therapy in treatment of different diseases. *Acta Med Iran* 2012; **50**: 79-96 [PMID: 22359076]

24 **Gandia C**, Armiñan A, García-Verdugo JM, Lledó E, Ruiz A, Miñana MD, Sanchez-Torrijos J, Payá R, Mirabet V, Carbonell-Uberos F, Llop M, Montero JA, Sepúlveda P. Human dental pulp stem cells improve left ventricular function, induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction. *Stem Cells* 2008; **26**: 638-645 [PMID: 18079433 DOI: 10.1634/stemcells.2007-0484]

25 **Perry BC**, Zhou D, Wu X, Yang FC, Byers MA, Chu TM, Hockema JJ, Woods EJ, Goebel WS. Collection, cryopreservation, and characterization of human dental pulp-derived mesenchymal stem cells for banking and clinical use. *Tissue Eng Part C Methods* 2008; **14**: 149-156 [PMID: 18489245 DOI: 10.1089/ten.tec.2008.0031]

26 **García-Olmo D**, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum* 2005; **48**: 1416-1423 [PMID: 15933795 DOI: 10.1007/s10350-005-0052-6]

27 **Ko CS**, Chen JH, Su WT. Stem Cells from Human Exfoliated Deciduous Teeth: A Concise Review. *Curr Stem Cell Res Ther* 2020; **15**: 61-76 [PMID: 31648649 DOI: 10.2174/1574888X14666191018122109]

28 **de Mendonça Costa A**, Bueno DF, Martins MT, Kerkis I, Kerkis A, Fanganiello RD, Cerruti H, Alonso N, Passos-Bueno MR. Reconstruction of large cranial defects in nonimmunosuppressed experimental design with human dental pulp stem cells. *J Craniofac Surg* 2008; **19**: 204-210 [PMID: 18216690 DOI: 10.1097/scs.0b013e31815c8a54]

29 **Seo BM**, Sonoyama W, Yamaza T, Coppe C, Kikuiri T, Akiyama K, Lee JS, Shi S. SHED repair critical-size calvarial defects in mice. *Oral Dis* 2008; **14**: 428-434 [PMID: 18938268 DOI: 10.1111/j.1601-0825.2007.01396.x]

30 **Mao JJ**. Stem cells and the future of dental care. *N Y State Dent J* 2008; **74**: 20-24 [PMID: 18450184]

31 **Shi S**, Bartold PM, Miura M, Seo BM, Robey PG, Gronthos S. The efficacy of mesenchymal stem

cells to regenerate and repair dental structures. *Orthod Craniofac Res* 2005; **8**: 191-199 [PMID: 16022721 DOI: 10.1111/j.1601-6343.2005.00331.x]

32 **Fu X**, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal Stem Cell Migration and Tissue Repair. *Cells* 2019; **8**: 784 [PMID: 31357692 DOI: 10.3390/cells8080784]

33 **Naderi N**, Combellack EJ, Griffin M, Sedaghati T, Javed M, Findlay MW, Wallace CG, Mosahebi A, Butler PE, Seifalian AM, Whitaker IS. The regenerative role of adipose-derived stem cells (ADSC) in plastic and reconstructive surgery. *Int Wound J* 2017; **14**: 112-124 [PMID: 26833722 DOI: 10.1111/iwj.12569]

34 **Grochowski C**, Radzikowska E, Maciejewski R. Neural stem cell therapy-Brief review. *Clin Neurol Neurosurg* 2018; **173**: 8-14 [PMID: 30053745 DOI: 10.1016/j.clineuro.2018.07.013]

35 **Vizoso FJ**, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. *Int J Mol Sci* 2017; **18**: 1852 [PMID: 28841158 DOI: 10.3390/ijms18091852]

36 **Bento G**, Shafigullina AK, Rizvanov AA, Sardão VA, Macedo MP, Oliveira PJ. Urine-Derived Stem Cells: Applications in Regenerative and Predictive Medicine. *Cells* 2020; **9**: 573 [PMID: 32121221 DOI: 10.3390/cells9030573]

37 **Ji X**, Wang M, Chen F, Zhou J. Urine-Derived Stem Cells: The Present and the Future. *Stem Cells Int* 2017; **2017**: 4378947 [PMID: 29250119 DOI: 10.1155/2017/4378947]

38 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]

39 **Sommer CA**, Mostoslavsky G. Experimental approaches for the generation of induced pluripotent stem cells. *Stem Cell Res Ther* 2010; **1**: 26 [PMID: 20699015 DOI: 10.1186/scrt26]

40 **Shi D**, Lu F, Wei Y, Cui K, Yang S, Wei J, Liu Q. Buffalos (Bubalus bubalis) cloned by nuclear transfer of somatic cells. *Biol Reprod* 2007; **77**: 285-291 [PMID: 17475931 DOI: 10.1095/biolreprod.107.060210]

41 **Zhou Q**, Brown J, Kanarek A, Rajagopal J, Melton DA. In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. *Nature* 2008; **455**: 627-632 [PMID: 18754011 DOI: 10.1038/nature07314]

42 **Hilfiker A**, Kasper C, Hass R, Haverich A. Mesenchymal stem cells and progenitor cells in connective tissue engineering and regenerative medicine: is there a future for transplantation? *Langenbecks Arch Surg* 2011; **396**: 489-497 [PMID: 21373941 DOI: 10.1007/s00423-011-0762-2]

43 **Yang Q**, Chen W, Zhang C, Xie Y, Gao Y, Deng C, Sun X, Liu G. Combined Transplantation of Adipose Tissue-Derived Stem Cells and Endothelial Progenitor Cells Improve Diabetic Erectile Dysfunction in a Rat Model. *Stem Cells Int* 2020; **2020**: 2154053 [PMID: 32714394 DOI: 10.1155/2020/2154053]

44 **Zhang C**, Luo D, Li T, Yang Q, Xie Y, Chen H, Lv L, Yao J, Deng C, Liang X, Wu R, Sun X, Zhang Y, Liu G. Transplantation of Human Urine-Derived Stem Cells Ameliorates Erectile Function and Cavernosal Endothelial Function by Promoting Autophagy of Corpus Cavernosal Endothelial Cells in Diabetic Erectile Dysfunction Rats. *Stem Cells Int* 2019; **2019**: 2168709 [PMID: 31582984 DOI: 10.1155/2019/2168709]

45 **Liu T**, Peng Y, Jia C, Fang X, Li J, Zhong W. Hepatocyte growth factor-modified adipose tissue-derived stem cells improve erectile function in streptozotocin-induced diabetic rats. *Growth Factors* 2015; **33**: 282-289 [PMID: 26339935 DOI: 10.3109/08977194.2015.1077825]

46 **Shan HT**, Zhang HB, Chen WT, Chen FZ, Wang T, Luo JT, Yue M, Lin JH, Wei AY. Combination of low-energy shock-wave therapy and bone marrow mesenchymal stem cell transplantation to improve the erectile function of diabetic rats. *Asian J Androl* 2017; **19**: 26-33 [PMID: 27427555 DOI: 10.4103/1008-682X.184271]

47 **Jung AR**, Park YH, Kim GE, Kim MY, Jeon SH, Kim HY, Kim SY, Oh SH, Lee JY. Stem Cell/Oxygen-Releasing Microparticle Enhances Erectile Function in a Cavernous Nerve Injury Model. *Tissue Eng Part A* 2021; **27**: 50-62 [PMID: 32122268 DOI: 10.1089/ten.TEA.2019.0240]

48 **Kimbrel EA**, Lanza R. Next-generation stem cells - ushering in a new era of cell-based therapies. *Nat Rev Drug Discov* 2020; **19**: 463-479 [PMID: 32612263 DOI: 10.1038/s41573-020-0064-x]

49 **Liu G**, Sun X, Bian J, Wu R, Guan X, Ouyang B, Huang Y, Xiao H, Luo D, Atala A, Zhang Y, Deng C. Correction of diabetic erectile dysfunction with adipose derived stem cells modified with the vascular endothelial growth factor gene in a rodent diabetic model. *PLoS One* 2013; **8**: e72790 [PMID: 24023647 DOI: 10.1371/journal.pone.0072790]

50 **Kizub IV**, Klymenko KI, Soloviev AI. Protein kinase C in enhanced vascular tone in diabetes mellitus. *Int J Cardiol* 2014; **174**: 230-242 [PMID: 24794552 DOI: 10.1016/j.ijcard.2014.04.117]

51 **Maiorino MI**, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. *Diabetes Metab Syndr Obes* 2014; **7**: 95-105 [PMID: 24623985 DOI: 10.2147/DMSO.S36455]

52 **Keshtkar S**, Azarpira N, Ghahremani MH. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. *Stem Cell Res Ther* 2018; **9**: 63 [PMID: 29523213 DOI: 10.1186/s13287-018-0791-7]

53 **Ullah M**, Ng NN, Concepcion W, Thakor AS. Emerging role of stem cell-derived extracellular microRNAs in age-associated human diseases and in different therapies of longevity. *Ageing Res Rev* 2020; **57**: 100979 [PMID: 31704472 DOI: 10.1016/j.arr.2019.100979]

54 **Sun X**, Meng H, Wan W, Xie M, Wen C. Application potential of stem/progenitor cell-derived extracellular vesicles in renal diseases. *Stem Cell Res Ther* 2019; **10**: 8 [PMID: 30616603 DOI:

10.1186/s13287-018-1097-5]
55 **Spees JL**, Lee RH, Gregory CA. Mechanisms of mesenchymal stem/stromal cell function. *Stem Cell Res Ther* 2016; **7**: 125 [PMID: 27581859 DOI: 10.1186/s13287-016-0363-7]
56 **Gnecchi M**, Danieli P, Malpasso G, Ciuffreda MC. Paracrine Mechanisms of Mesenchymal Stem Cells in Tissue Repair. *Methods Mol Biol* 2016; **1416**: 123-146 [PMID: 27236669 DOI: 10.1007/978-1-4939-3584-0_7]
57 **Nooshabadi VT**, Mardpour S, Yousefi-Ahmadipour A, Allahverdi A, Izadpanah M, Daneshimehr F, Ai J, Banafshe HR, Ebrahimi-Barough S. The extracellular vesicles-derived from mesenchymal stromal cells: A new therapeutic option in regenerative medicine. *J Cell Biochem* 2018; **119**: 8048-8073 [PMID: 29377241 DOI: 10.1002/jcb.26726]
58 **Chen F**, Zhang H, Wang Z, Ding W, Zeng Q, Liu W, Huang C, He S, Wei A. Adipose-Derived Stem Cell-Derived Exosomes Ameliorate Erectile Dysfunction in a Rat Model of Type 2 Diabetes. *J Sex Med* 2017; **14**: 1084-1094 [PMID: 28781215 DOI: 10.1016/j.jsxm.2017.07.005]
59 **Ouyang B**, Xie Y, Zhang C, Deng C, Lv L, Yao J, Zhang Y, Liu G, Deng J. Extracellular Vesicles From Human Urine-Derived Stem Cells Ameliorate Erectile Dysfunction in a Diabetic Rat Model by Delivering Proangiogenic MicroRNA. *Sex Med* 2019; **7**: 241-250 [PMID: 30910509 DOI: 10.1016/j.esxm.2019.02.001]
60 **Bahk JY**, Jung JH, Han H, Min SK, Lee YS. Treatment of diabetic impotence with umbilical cord blood stem cell intracavernosal transplant: preliminary report of 7 cases. *Exp Clin Transplant* 2010; **8**: 150-160 [PMID: 20565373]
61 **Levy JA**, Marchand M, Iorio L, Cassini W, Zahalsky MP. Determining the Feasibility of Managing Erectile Dysfunction in Humans With Placental-Derived Stem Cells. *J Am Osteopath Assoc* 2016; **116**: e1-e5 [PMID: 26745574 DOI: 10.7556/jaoa.2016.007]
62 **Yiou R**, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, Khodari M, Rodriguez AM, Augustin D, Roudot-Thoraval F, de la Taille A, Rouard H. Safety of Intracavernous Bone Marrow-Mononuclear Cells for Postradical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study. *Eur Urol* 2016; **69**: 988-991 [PMID: 26439886 DOI: 10.1016/j.eururo.2015.09.026]
63 **Yiou R**, Hamidou L, Birebent B, Bitari D, Le Corvoisier P, Contremoulins I, Rodriguez AM, Augustin D, Roudot-Thoraval F, de la Taille A, Rouard H. Intracavernous Injections of Bone Marrow Mononucleated Cells for Postradical Prostatectomy Erectile Dysfunction: Final Results of the INSTIN Clinical Trial. *Eur Urol Focus* 2017; **3**: 643-645 [PMID: 28753830 DOI: 10.1016/j.euf.2017.06.009]
64 **Al Demour S**, Jafar H, Adwan S, AlSharif A, Alhawari H, Alrabadi A, Zayed A, Jaradat A, Awidi A. Safety and Potential Therapeutic Effect of Two Intracavernous Autologous Bone Marrow Derived Mesenchymal Stem Cells injections in Diabetic Patients with Erectile Dysfunction: An Open Label Phase I Clinical Trial. *Urol Int* 2018; **101**: 358-365 [PMID: 30173210 DOI: 10.1159/000492120]
65 **Haahr MK**, Harken Jensen C, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, Sheikh SP, Lund L. A 12-Month Follow-up After a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial. *Urology* 2018; **121**: 203.e6-203. e13 [PMID: 29958973 DOI: 10.1016/j.urology.2018.06.018]
66 **Li M**, Li H, Ruan Y, Wang T, Liu J. Stem Cell Therapy for Diabetic Erectile Dysfunction in Rats: A Meta-Analysis. *PLoS One* 2016; **11**: e0154341 [PMID: 27111659 DOI: 10.1371/journal.pone.0154341]
67 **Albersen M**, Fandel TM, Lin G, Wang G, Banie L, Lin CS, Lue TF. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. *J Sex Med* 2010; **7**: 3331-3340 [PMID: 20561166 DOI: 10.1111/j.1743-6109.2010.01875.x]
68 **Sun C**, Lin H, Yu W, Li X, Chen Y, Qiu X, Wang R, Dai Y. Neurotrophic effect of bone marrow mesenchymal stem cells for erectile dysfunction in diabetic rats. *Int J Androl* 2012; **35**: 601-607 [PMID: 22428616 DOI: 10.1111/j.1365-2605.2012.01250.x]
69 **Reed-Maldonado AB**, Lue TF. The Current Status of Stem-Cell Therapy in Erectile Dysfunction: A Review. *World J Mens Health* 2016; **34**: 155-164 [PMID: 28053944 DOI: 10.5534/wjmh.2016.34.3.155]
70 **Yan H**, Ding Y, Lu M. Current Status and Prospects in the Treatment of Erectile Dysfunction by Adipose-Derived Stem Cells in the Diabetic Animal Model. *Sex Med Rev* 2020; **8**: 486-491 [PMID: 31980404 DOI: 10.1016/j.sxmr.2019.09.006]
71 **Brennen WN**, Zhang B, Kulac I, Kisteman LN, Antony L, Wang H, Meeker AK, De Marzo AM, Garraway IP, Denmeade SR, Isaacs JT. Mesenchymal stem cell infiltration during neoplastic transformation of the human prostate. *Oncotarget* 2017; **8**: 46710-46727 [PMID: 28493842 DOI: 10.18632/oncotarget.17362]
72 **Casiraghi F**, Remuzzi G, Abbate M, Perico N. Multipotent mesenchymal stromal cell therapy and risk of malignancies. *Stem Cell Rev Rep* 2013; **9**: 65-79 [PMID: 22237468 DOI: 10.1007/s12015-011-9345-4]
73 **Mangir N**, Akbal C, Tarcan T, Simsek F, Turkeri L. Mesenchymal stem cell therapy in treatment of erectile dysfunction: autologous or allogeneic cell sources? *Int J Urol* 2014; **21**: 1280-1285 [PMID: 25074479 DOI: 10.1111/iju.12585]
74 **Huang XP**, Sun Z, Miyagi Y, McDonald Kinkaid H, Zhang L, Weisel RD, Li RK. Differentiation of allogeneic mesenchymal stem cells induces immunogenicity and limits their long-term benefits for

myocardial repair. *Circulation* 2010; **122**: 2419-2429 [PMID: 21098445 DOI: 10.1161/CIRCULATIONAHA.110.955971]

75 **You D**, Jang MJ, Lee J, Jeong IG, Kim HS, Moon KH, Suh N, Kim CS. Periprostatic implantation of human bone marrow-derived mesenchymal stem cells potentiates recovery of erectile function by intracavernosal injection in a rat model of cavernous nerve injury. *Urology* 2013; **81**: 104-110 [PMID: 23122545 DOI: 10.1016/j.urology.2012.08.046]

76 **Mohr A**, Zwacka R. The future of mesenchymal stem cell-based therapeutic approaches for cancer - From cells to ghosts. *Cancer Lett* 2018; **414**: 239-249 [PMID: 29175461 DOI: 10.1016/j.canlet.2017.11.025]

77 **Assis AC**, Carvalho JL, Jacoby BA, Ferreira RL, Castanheira P, Diniz SO, Cardoso VN, Goes AM, Ferreira AJ. Time-dependent migration of systemically delivered bone marrow mesenchymal stem cells to the infarcted heart. *Cell Transplant* 2010; **19**: 219-230 [PMID: 19906330 DOI: 10.3727/096368909X479677]

78 **Barbash IM**, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes LH, Kloner RA, Leor J. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation* 2003; **108**: 863-868 [PMID: 12900340 DOI: 10.1161/01.CIR.0000084828.50310.6A]

79 **Fischer UM**, Harting MT, Jimenez F, Monzon-Posadas WO, Xue H, Savitz SI, Laine GA, Cox CS Jr. Pulmonary passage is a major obstacle for intravenous stem cell delivery: the pulmonary first-pass effect. *Stem Cells Dev* 2009; **18**: 683-692 [PMID: 19099374 DOI: 10.1089/scd.2008.0253]

80 **Lee RH**, Yoon N, Reneau JC, Prockop DJ. Preactivation of human MSCs with TNF-α enhances tumor-suppressive activity. *Cell Stem Cell* 2012; **11**: 825-835 [PMID: 23142520 DOI: 10.1016/j.stem.2012.10.001]

81 **Lee RH**, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, Semprun-Prieto L, Delafontaine P, Prockop DJ. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. *Cell Stem Cell* 2009; **5**: 54-63 [PMID: 19570514 DOI: 10.1016/j.stem.2009.05.003]

82 **Uccelli A**, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008; **8**: 726-736 [PMID: 19172693 DOI: 10.1038/nri2395]

83 **Wu H**, Tang WH, Zhao LM, Liu DF, Yang YZ, Zhang HT, Zhang Z, Hong K, Lin HC, Jiang H. Nanotechnology-assisted adipose-derived stem cell (ADSC) therapy for erectile dysfunction of cavernous nerve injury: *In vivo* cell tracking, optimized injection dosage, and functional evaluation. *Asian J Androl* 2018; **20**: 442-447 [PMID: 30004040 DOI: 10.4103/aja.aja_48_18]

84 **de Miguel-Beriain I**. The ethics of stem cells revisited. *Adv Drug Deliv Rev* 2015; **82-83**: 176-180 [PMID: 25446134 DOI: 10.1016/j.addr.2014.11.011]

85 **U.S. Department of Health and Human Services**, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for human somatic cell therapy and gene therapy. *Hum Gene Ther* 2001; **12**: 303-314 [PMID: 11177566 DOI: 10.1089/10430340150218431]

86 **Daley GQ**, Hyun I, Apperley JF, Barker RA, Benvenisty N, Bredenoord AL, Breuer CK, Caulfield T, Cedars MI, Frey-Vasconcells J, Heslop HE, Jin Y, Lee RT, McCabe C, Munsie M, Murry CE, Piantadosi S, Rao M, Rooke HM, Sipp D, Studer L, Sugarman J, Takahashi M, Zimmerman M, Kimmelman J. Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines. *Stem Cell Reports* 2016; **6**: 787-797 [PMID: 27185282 DOI: 10.1016/j.stemcr.2016.05.001]

87 **Moradi S**, Mahdizadeh H, Šarić T, Kim J, Harati J, Shahsavarani H, Greber B, Moore JB 4th. Research and therapy with induced pluripotent stem cells (iPSCs): social, legal, and ethical considerations. *Stem Cell Res Ther* 2019; **10**: 341 [PMID: 31753034 DOI: 10.1186/s13287-019-1455-y]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com