ISSN 1948-0210 (online)

World Journal of *Stem Cells*

World J Stem Cells 2021 October 26; 13(10): 1360-1609

Published by Baishideng Publishing Group Inc

World Journal of Stem Cells

Contents

Monthly Volume 13 Number 10 October 26, 2021

ABOUT COVER

Editorial Board Member of *World Journal of Stem Cells*, Hong-Cui Cao, MD, PhD, Professor, Vice Director, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. hccao@zju.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc*.

INDEXING/ABSTRACTING

The *WJSC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, BIOSIS Previews, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJSC* as 5.326; IF without journal self cites: 5.035; 5-year IF: 4.956; Journal Citation Indicator: 0.55; Ranking: 14 among 29 journals in cell and tissue engineering; Quartile category: Q2; Ranking: 72 among 195 journals in cell biology; and Quartile category: Q2. The *WJSC*'s CiteScore for 2020 is 3.1 and Scopus CiteScore rank 2020: Histology is 31/60; Genetics is 205/325; Genetics (clinical) is 64/87; Molecular Biology is 285/382; Cell Biology is 208/279.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yan-Xia Xing*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Ze-Mao Gong*.

NAME OF JOURNAL
World Journal of Stem Cells

ISSN
ISSN 1948-0210 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shengwen Calvin Li, Tong Cao, Carlo Ventura

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-0210/editorialboard.htm

PUBLICATION DATE
October 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

WJSC World Journal of Stem Cells

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

World J Stem Cells 2021 October 26; 13(10): 1549-1563

DOI: 10.4252/wjsc.v13.i10.1549

ISSN 1948-0210 (online)

MINIREVIEWS

Stem cell therapy and diabetic erectile dysfunction: A critical review

Cennikon Pakpahan, Raditya Ibrahim, William William, Zakiyatul Faizah, Juniastuti Juniastuti, Maria I Lusida, Delvac Oceandy

ORCID number: Cennikon Pakpahan 0000-0003-0157-1131; Raditya Ibrahim 0000-0002-9168-4959; William William 0000-0002-9852-5686; Zakiyatul Faizah 0000-0003-0962-9123; Juniastuti Juniastuti 0000-0002-1437-640X; Maria I Lusida 0000-0001-5039-0674; Delvac Oceandy 0000-0002-6242-6491.

Author contributions: Pakpahan C, Ibrahim R and William W performed literature search and review, and wrote the manuscript; Faizah Z, Juniastuti J and Lusida MI reviewed the manuscript; Oceandy D supervised the literature review and edited manuscript.

Supported by Mandate Research Grant from Universitas Airlangga, No. 1408/UN3/2019.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Cennikon Pakpahan, Zakiyatul Faizah, Department of Biomedical Sciences, Universitas Airlangga, Surabaya 60132, Indonesia

Cennikon Pakpahan, Raditya Ibrahim, William William, Andrology Program, Universitas Airlangga, Surabaya 60132, Indonesia

William William, Department of Medical Biology, School of Medicine and Health Sciences Atma Jaya Catholic University of Indonesia, Jakarta 14440, Indonesia

Juniastuti Juniastuti, Institute of Tropical Disease, Universitas Airlangga, Surabaya 60132, Indonesia

Maria I Lusida, Institute for Tropical Disease, Universitas Airlangga, Surabaya 60132, Indonesia

Delvac Oceandy, Division of Cardiovascular Sciences, The University of Manchester, Manchester Academic Health Science Centre, Manchester M13 9PT, United Kingdom

Corresponding author: Delvac Oceandy, MD, PhD, Reader (Associate Professor), Division of Cardiovascular Sciences, The University of Manchester, Manchester Academic Health Science Centre, Street Address, Manchester M13 9PT, United Kingdom. delvac.oceandy@manchester.ac.uk

Abstract

Erectile dysfunction (ED) has been identified as one of the most frequent chronic complications of diabetes mellitus (DM). The prevalence of ED is estimated to be about 67.4% in all DM cases worldwide. The pathophysiological process leading to ED involves endothelial, neurological, hormonal, and psychological factors. In DM, endothelial and neurological factors play a crucial role. Damages in the blood vessels and erectile tissue due to insulin resistance are the hallmark of ED in DM. The current treatments for ED include phosphodiesterase-5 inhibitors and penile prosthesis surgery. However, these treatments are limited in terms of just relieving the symptoms, but not resolving the cause of the problem. The use of stem cells for treating ED is currently being studied mostly in experimental animals. The stem cells used are derived from adipose tissue, bone, or human urine. Most of the studies observed an improvement in erectile quality in the experimental animals as well as an improvement in erectile tissue. However, research on stem cell therapy for ED in humans remains to be limited. Nevertheless, significant findings from studies using animal models indicate a potential use of stem cells in the treatment of ED.

Manuscript source: Invited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: Indonesia

Peer-review report's scientific quality classification

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

Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: April 19, 2021
Revised: May 4, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: October 26, 2021

P-Reviewer: Nong X
S-Editor: Gao CC
L-Editor: A
P-Editor: Zhang YL

Key Words: Stem cells; Diabetes mellitus; Erectile dysfunction; Stem cell therapy; Diabetic erectile dysfunction

Core Tip: Erectile dysfunction (ED) is one of the most frequent complications of diabetes mellitus in males, which interferes with the patient's quality of life. Current available treatments, whilst improve the symptoms, are not able to repair damages of the affected tissues. Stem cells have the potential ability to renew and repair damaged endothelial cells and penile tissue in the diabetic ED. Recent studies have provided promising results on the use of stem cells to treat this condition. This article reviews current advances on this area of research.

Citation: Pakpahan C, Ibrahim R, William W, Faizah Z, Juniastuti J, Lusida MI, Oceandy D. Stem cell therapy and diabetic erectile dysfunction: A critical review. *World J Stem Cells* 2021; 13(10): 1549-1563
URL: https://www.wjgnet.com/1948-0210/full/v13/i10/1549.htm
DOI: https://dx.doi.org/10.4252/wjsc.v13.i10.1549

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to attain or maintain an adequate erection to reach satisfaction in sexual intercourse[1]. Although this condition does not directly coincide with serious health problems, it correlates with the decline in the quality of life[2]. Moreover, ED has been determined to be more common in men with diabetes mellitus (DM). Previous studies have shown that the prevalence of ED in DM is very high, *i.e.*, at 67.4%, among those with DM[3]. Thus, DM can be regarded as a major risk factor for acquiring sexual dysfunction in men, increasing the risk of ED in men with DM three times higher than that in those without diabetes[4].

MECHANISM OF DIABETIC ED

Erection is a condition when the penile organ becomes rigid and elevated as a result of the erectile tissue being filled with blood. It is modulated by several mechanisms involving endothelial cells and the autonomic nervous function. To better understand the pathogenesis of ED, we need to comprehend the physiological process of erection, as discussed briefly below.

Three key processes occur during erection: (1) The neurologically mediated arterial inflow; (2) The relaxation of smooth muscle within the corpora spongiosa to allow the blood to fill the penile vasculature; and (3) The obstruction of the veins to retain the blood within the penile vasculature[5].

In response to sexual stimuli, the brain transmits parasympathetic signals through the spinal cord. The signal then reaches the non-adrenergic non-cholinergic neuronal terminals, which will then induce the production of nitric oxide (NO) by neuronal NO synthase (nNOS). Likewise, the endothelium also produces NO *via* the activation of endothelial NO synthase (eNOS). eNOS and nNOS act as the endothelial and neuronal regulators, respectively. Then, the NO will be transported to the corpora spongiosa where it converts GTP to cyclic guanosine monophosphate (cGMP) with the help of the guanylate cyclase enzyme. The cGMP induces smooth muscle relaxation, allowing arterial flow to fill the cavernosal space. cGMP also potentiates protein kinase G activity that leads to free intracellular calcium being taken up by the endoplasmic reticulum, causing a decrease in calcium flux and an increase in potassium flux from the cells and in turn causing depolarization followed by the relaxation of vascular smooth muscle. When the cavernosal space congests with blood, the veins become compressed and occluded which traps the blood in the cavernosal space during tumescence[1,5,6].

Based on its mechanism, the pathological causes of diabetic-induced ED can be classified into several different categories, *i.e.*, endothelial, neuronal, and endocrinal causes and others, such as psychological and diabetic-related infections and multiple drug prescriptions. However, all of these dysfunctions can intertwine to form ED (Figure 1).

Endothelial factors

One of the most important factors that contribute to the development of diabetic ED is endothelial dysfunction. Endothelial dysfunction is primarily characterized by the loss of NO biological activity and/or biosynthesis at the cellular level, but it may also refer to the reduction in endothelial-dependent vasodilatory response of the smooth muscle cells[7]. The reduction in NO bioavailability is primarily caused by the reduced activity and/or low level of eNOS expression. One possible factor that affects the impairment of eNOS function in diabetic ED is the specific glycosylation process that incapacitates the activation of vascular endothelial growth factor (VEGF) signaling[8]. VEGF is proven to be a survival factor for endothelial cells[9] and also contributes to the upregulation of eNOS expression at the molecular level[10]. Despite its important role in modulating eNOS function, it seems that VEGF is not involved in the regulation of nNOS[11,12]. Meanwhile, the role of the RhoA-ROCK (Rho-associated protein kinase) complex in the development of ED has also been comprehensively studied in the past few years. ROCK, which is activated by RhoA, regulates myosin light chain phosphatase (MLCP) *via* phosphorylation. This leads to the deactivation of MLCP and subsequently promotes the contraction of the cavernosal body by lowering the levels of calcium in smooth muscles, facilitating the chronic-tonic contraction, thus maintaining the flaccid state of the penis[13]. ROCK has two isoforms: ROCK-1 and ROCK-2. Chiou *et al*[14] have shown that the induction of type 2 diabetes in rats resulted in the downregulation of eNOS, nNOS, and protein kinase G and the upregulation of the RhoA-ROCK pathway, particularly ROCK-1 isoform. Recently, studies have been conducted to assess the effects of ROCK inhibitors on diabetic ED. Treatment with ROCK inhibitors (SAR407899) has been found to induce penile erection through mechanisms independent of eNOS activity. Thus, this treatment can be targeted to cases of diabetic ED where eNOS activity is impaired[14].

The RhoA-ROCK pathway is also linked with the endothelin-1 (ET1)-induced vasoconstriction[15]. ET1 is a powerful vasoconstrictor, which is released from the penile vascular endothelium. In diabetic patients, the level of plasma ET1 is high[16], which may induce the constriction of the penile blood vessels. ET1 Level may also be elevated in response to the increase in oxidative stress in DM. Chronic hyperglycemia induces the release of free radicals (reactive oxidative species) due to the formation of advanced glycation end products (AGEs). This may contribute to the development of diabetic ED through oxidative cell damage and the suppression of NO action[17,18].

These processes will affect the elasticity of the blood vessels. This may be crucial in the development of ED since elastic blood vessels are important to enable better erections. Moreover, endothelial damage can cause plaque formation and subsequently the blockage of blood vessels. This blockage will result in the inability of the blood vessels to expand properly, thus leading to lower blood capacity and decreased speed of blood flow, resulting in reduced erectile ability.

Neuronal factors

The neuronal aspects of diabetic ED are less well understood due to lacking diagnostic tools available to support this etiology. Several studies have been conducted to assess nocturnal penile erection and whole sexual cycle *via* magnetic resonance imaging and positron emission tomography scan to characterize the disorder in the central aspects of erection[19]. Diabetic neuropathy is proven to be an important factor in the development of diabetic ED.

In DM, microangiopathy and nerve damage are caused by increased oxidative stress, accumulation of AGEs, impaired axonal transport, increased flux through the polyol pathway, altered protein kinase C activity, and poly(ADP-ribose) polymerase activity[20]. In a study comparing the significant microangiopathy and macroangiopathy factors in DM, the results indicated that microangiopathy factors, especially diabetic neuropathy, have a more significant impact than macroangiopathy factors in the development of diabetic ED[6].

Endocrine factors

Hypogonadotropic hypogonadism occurs in approximately 30%-40% of men with type 2 diabetes[21]. This condition reduces the production of testosterone, which has been identified to stimulate the synthesis, storage, and release of pro-erectogenic

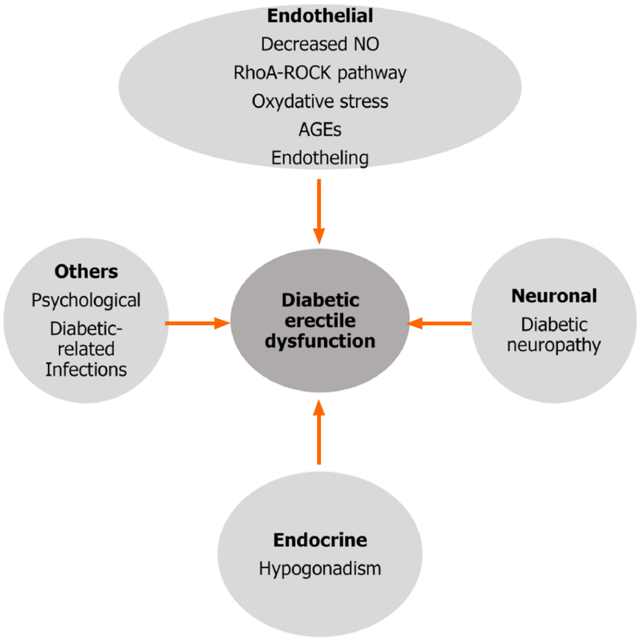

Figure 1 Factors that affect diabetic erectile dysfunction. Major factors that affect the development of diabetic erectile dysfunction include endothelial damage, neuronal dysfunction and endocrine abnormality. Other factors such as psychological factor and diabetic-related infections may also affect the development of diabetic erectile dysfunction. NO: Nitric oxide; AGEs: Advanced glycation end products.

neurotransmitters; modulate neuronal activity, receptor sensitivity, neurotransmitter liberation, and socio-sexual behavior (increasing libido); and positively influence the levels of dopamine, NO, oxytocin, *etc.*[1]. In a population-based cohort, the prevalence of hypogonadism in men with ED was 35% compared with 22.7% in men without ED [22]. A study in Japan conducted by Imai *et al*[23] showed that decreased testosterone has been associated with severe or moderate ED as opposed to men with mild or no ED and is a risk factor for the development of ED.

EVALUATION OF ED

Decreased erectile capacity is the most common symptom of patients with ED. The standard way to evaluate ED is by using the International Index of Erectile Function-5 (IIEF-5) or Erectile Hardness Score (EHS) criteria. IIEF-5 has five questions that can be used to evaluate a person's sexual life. This questionnaire has a sensitivity of 98% and a specificity of 88%[24].

Moreover, the EHS scoring system can also be used to evaluate the progression of ED following treatment as this scale is convenient to use. The EHS scale categorizes ED into five levels of erectile ability: (1) If the penis does not change; (2) If the penis is slightly enlarged without hardening; (3) If the penis is enlarged and hardens but cannot be used for sexual intercourse; (4) When the penis is enlarged, hardens, and can be used for sexual intercourse, but not maximally; and (5) If the penis is enlarged and hardens to the maximum[25].

In various studies using experimental animals, the evaluation of ED can be performed at the molecular and tissue level, starting from intracavernosal pressure measurement, assessment of angiogenesis process using certain markers, and analysis of erectile tissue profile including the blood vessel content and smooth muscle structure. Other molecular processes can also be used as parameters in the evaluation of ED.

TREATMENT APPROACHES OF DIABETIC ED

Lifestyle modifications

In an effort to regain the capability of erection in diabetic ED, many approaches in terms of lifestyle change have to be applied. Long-term control of glycemic levels is important. Using HbA1c as an index of hyperglycemia, Cho *et al*[26] showed a significant connection between the severity of ED and the level of HbA1c. Physical activity has beneficial effects on the prevention and/or improvement of ED in several prospective studies[27]. With regard to consistent physical activity, weight loss in obese or overweight diabetic patients is strongly correlated with ED, as observed in a prospective study with a study duration of 5 years to 25 years showing that overweight and obese individuals displayed an increased probability in developing ED compared to individuals with normal weight[28]. Importantly, smoking[5] and alcohol appear to be risk factors for ED. In a recent study focusing on alcohol intake and erectile function, it was shown that moderate alcohol consumption conferred the highest protection of erectile function[29].

Pharmacological approach

Phosphodiesterase-5 (PDE5) inhibitors are the first-line therapy for treating ED. The mechanism of the PDE5 inhibitor drug is to inhibit the PDE5 enzyme in vascular smooth muscle cells, thus preventing cGMP degradation to GMP resulting in a sustained erection as the penile blood vessels will be kept dilated. Currently, there are four different types of PDE5 inhibitors available for ED treatment: sildenafil, vardenafil, tadalafil, and avanafil[5].

The most common adverse effects related to the treatment with PDE5 inhibitors are headache and flushing due to the vasodilatory effects of PDE5 inhibitors on the blood vessels. Abnormal vision is experienced by about 6% of individuals taking sildenafil, which could be attributed to the inhibitory action of the drug against PDE6, which is abundant in the retina[5]. On the other hand, back pain and muscle cramps are common adverse effects of tadalafil[5].

In the early 1980s, the first report of intracavernosal injection with papaverine was published and opened a new line of treatment of ED[30]. This second line of treatment is normally used for patients who demonstrated low response or low effectivity or those displaying severe side effects following PDE5 inhibitor treatment. Drugs that are available for ICI are alprostadil (10 mcg, 20 mcg, 40 mcg) and papaverine. ICI treatment induces vasodilation in the arterial smooth muscles, inducing blood flow and blood entrapment within the lacunar spaces of the penis. This treatment has shown better efficacy than oral pharmacological treatment. However, the dropout rate for ICI therapy remains relatively high, and it may be associated with priapism, ecchymoses, hematoma formation, and penile fibrosis[31]. The intraurethral application of alprostadil is also used for second line treatments of ED[30]. The most common side effects of this therapy are penile pain and urethral burning sensation.

Vacuum and surgical approach

Vacuum therapy uses negative pressure to distend the corporal sinusoids and to increase blood inflow to the penis[32]. However, studies that evaluate the use of vacuum constriction device (VCD) reported up to 30% patient dropout due to inadequate rigidity, penile pain, difficulty to ejaculate, and aesthetic causes[33].

The implantation of penile prosthesis as a surgical therapeutic approach for ED is used when the pharmacological (oral, injection, or trans-urethral) and mechanical (VCD) approaches do not achieve satisfactory effects or induce side effects that bothered the patient. The implantation of prosthesis provides a reliable and predictable erection and the highest satisfaction rate to both partners when compared with all of the treatments in ED[34].

All of the treatments available for diabetic ED are developed to achieve sexual satisfaction by improving the erection, but none of them have the capacity to repair the endothelial blood vessels in patients with diabetic ED. New therapeutic strategies to address the main problem in ED, for example, regenerative therapy, have not been widely explored, despite their potential to improve endothelial function. Regenerative therapy, such as stem cell-based therapy, has been identified to have the potential to address the root of the problem in diabetic ED. In the next part of this review, we discuss this therapeutic approach for the treatment for diabetic ED.

STEM CELLS AS A FUTURE THERAPY FOR DIABETIC ED

Ernst Haeckel first introduced stem cells (*stammzelle* in German) in 1868 to delineate unicellular organism from which all multicellular organisms originated[35]. Since then, many studies were conducted to identify different types of stem cells and their potency to treat various human diseases. In 2006, Yamanaka successfully developed induced pluripotent stem cells (iPSCs), which were derived from adult somatic cell reprogramming, increasing the hope of using this type of stem cells as a therapeutic approach for many chronic diseases[35]. Stem cells are unique because they have several features such as the capability to self-renew, extensive proliferation capacity, the potential to differentiate to different cell types, the ability to minimize DNA damage through several DNA repair system, and the ability to maintain a very low metabolism to reduce reactive oxygen species level (quiescent stem cells)[35-37].

Classification of stem cells

Stem cells are undifferentiated cells which are able to differentiate to specialized cell types because of their ability to self-renew and to differentiate to one or more cell lineages. Stem cells can be classified based on their origin and potency[36,38]. To date, adipose-derived mesenchymal stem cell (ADSC) is considered as one of the most frequent cells used in the field of uro-andrology because it is abundant and easy to obtain[39-41]. Moreover, ADSCs have anti-inflammatory properties and an ability to repair vascular and nerve damage, which are the hallmarks in the development of diabetic ED[42].

Three fundamental aspects in stem cell therapy, including that for diabetic ED, need to be considered. These include (1) the origin of the stem cells, tissue biopsy, and cell harvesting, (2) *ex vivo* stem cell culture and clonal expansion through numerous distinct growth signals to produce specified cell type that we need, and (3) the delivery of these stem cells to the organ of interest[38,40].

Different routes of delivery are still being investigated to determine which one gives the best results. So far, several preclinical and clinical trials using various stem cell types have been conducted.

After delivery, two different mechanisms may occur in the tissues following stem cell implantation. First, the stem cells may differentiate to specific cells and hence, regenerate the damaged tissue. Second, stem cells may secrete various growth factors through the paracrine pathway[40,43], which can induce propagation and the differentiation of resident progenitor cells resulting in the repair of damaged tissue[43].

Current progress in stem cell therapy for diabetic ED

We have described that there are currently three main approaches to ED therapy which have been adopted worldwide, these are oral medication, intra-cavernosal injection and vacuum devices and penile prosthesis. However, all of these available options can only ameliorate the symptoms without restoring the damage of the penile tissue[39]. Stem cell therapy may address this problem.

The use of stem cells for the treatment of ED has been developed in several cases of ED post-prostatectomy. Several studies have reported many cases of cavernous nerve damage following prostatectomy[44], and the use of stem cells is now being investigated for the treatment of diabetic ED. It is estimated that ED occurs in approximately 67.4% of all cases of DM[3], illustrating that ED requires effective treatment to improve the quality of life of many patients with diabetes affected with ED.

Erection occurs as a result of the release of NO from sinusoidal endothelial cell walls. The vasodilation that occurs in these blood vessels in response to NO causes the compression of venules located between the trabecula and the tunica albuginea so that the blood becomes trapped within the blood vessels[43]. In simpler terms, it can be described that endothelial cells, cavernous smooth muscle cells, NO and nerve cells are key factors in erection, and DM damages these components. Stem cells, which have the ability to differentiate to specialised cells, may have the ability to correct these defects and restore proper erectile function[43]. This is the rationale for using stem cells as a therapy for ED in the future. However, the underlying mechanism still cannot be fully explained and needs further exploration.

Stem cell research in cases of ED has been pursued since the 2000s. However, most studies were limited to experimental animals. Of the 25 studies reviewed in this article, we found that 21 were conducted on animals (Table 1) and four on humans (Table 2). Of those experiments on animals, the stem cells used were isolated from adipose tissue, bone and human urine. Further, the type of stem cells used was autologous and allogenic, and the average number of stem cells injected per animal was 1×10^6 cells, which were delivered intra-cavernosally. However, the number of cells injected among these studies ranged from 2×10^6 to 5×10^5 cells per animal[46,47]. Moreover, in addition to stem cell therapy, several studies added growth factors, hormones and drugs, including insulin[48], magnetic iron oxide nanoparticles[49], microtissue[50], inducible NOS[47], myocardin[51], icariin[52], corin[53], exosomes from corpus cavernosum smooth muscle cells[54], fibroblast growth factor 2 (FGF2)[55], stromal cell-derived cell factor-1 (SDF-1)[56], VEGF[57] and hepatocyte growth factor[45].

Table 1 List of articles on stem cell therapy in animal models of diabetic erectile dysfunction

Ref.	Animal model (species, age, *n* number)	ED model	Evidence of previous DE	Type of stem cell	Source of stem cell	Characterization of stem cell	Number of cells injected and site of injection	Modification	Duration of follow-up	Parameter of therapy	Conclusion
Garcia *et al*[68]	10-wk-old Zucker (fa/fa) rats; *n* = 10 in each group (ADSCs and control)	Obese and type 2 diabetic rats with ED	Yes, CN electrostimulation	ADSCs; Autologous	Perigonadal adipose tissue	Not clear	1×10^6/IC	None	3 wk	ICP-MAP, nNOS, corporal body collagen, and corporal body endothelial cell	ADSCs improve ED
Liu *et al* [57]	10-wk-old male Sprague-Dawley rats; *n* = 12 in each group (lentivirus-VEGF, GFP ADSCs, VEGF/GFP ADSCs, control)	Type 1 diabetes induced by streptozotocin with ED	Yes, APO procedure	ADSCs; Allogenic	Bilateral groin	Yes, by flow cytometry	1×10^6/IC	VEGF, GFP	3 wk	ICP-MAP, VEGF, and e-NOS *in vivo* Endothelial, smooth muscle, and pericyte marker	Injection of ADSCs expressing VEGF displayed more efficiently and significantly raised ICP-MAP and increased endothelial markers
Ouyang *et al*[55]	Male Sprague-Dawley rats unspecific age; *n* = 10 in control group, *n* = 15 in each treatment group (USCs, lentivirus FGF2, USCs-FGF2)	High-fat diet following streptozotocin-induced diabetes	Yes, APO procedure	HUDSCs	Human urine	Yes, flow cytometry (CD24, CD29, CD31, CD34, CD44, CD45, CD73, CD90, CD105, CD146)	1×10^6/IC	FGF-2	4 wk	ICP-MAP, expression of endothelial markers (CD31, VEGF, and eNOS), smooth muscle markers (desmin and smoothelin), histological changes	USCs or USCs-FGF2 improved erectile function in type 2 diabetic rats
Li *et al*[69]	8-wk-old BALB/c mice; *n* = 8 in each group (control and treatment)	Streptozotocin-induced diabetes with ED	Not clear	BMSCs; Allogenic	Unspecified bone marrow	Yes, by flow cytometry. Identification with Sca-1 micromagnetic, identification of CD29, CD44, CD13, and CD34	Not mentioned	None	3 wk	ICP-MAP, penile histology	Flk-1 Sca-1 MSCs differentiate into skeletal and endothelial cells *in vivo* and *in vitro*
Liu *et al* [45]	Male Sprague-Dawley rats with no mentioned age; *n* = 10 in each group (negative control, ADSCs, ADSCs + hepatocyte growth factor)	Streptozotocin-induced diabetes with ED	Not clear	ADSCs	Not mentioned	Yes	2×10^6/IC	Hepatocyte growth factor	4 wk	ICP-MAP, smooth muscle, and endothelium (PECAM-1, SMA), apoptotic index	Significantly enhance the erectile function
Wang *et al*[70]	10-wk-old Male Sprague-Dawley rats; *n* = 15-16 in each group (control, normoxia AMCS, and hypoxia AMCS)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs; Allogenic	Inguinal adipose	Yes, fluorescent-activated cell sorting (CD90, CD29, CD34, CD45)	1×10^6/IC	Normoxia-hypoxia	4 wk	ICP-MAP, n-NOS, endothelial and smooth muscle histology	Hypoxia AMSCs improved ICP-MAP, nNOS. Hypoxia AMSCs condition effective to enhance theuraphetic effect of ED

Kovanecz *et al*[71]	7-mo-old Zucker (fa/fa) rats; *n* = 8 in each group (untreated, early diabetic treated with SC, early diabetic with high glucose treated with SC, late diabetic treated with SC, non-diabetic untreated)	Not mentioned specifically	Not clear	MSDCs; Allogenic	Hindlimb muscles	Not clear	1×10^6/IC	Early and late diabetes	8 wk	ICP-MAP, nNOS-eNOS, collagen ratio, calponin, inflammation marker	Stem cell decreased collagen and fat infiltration, upregulated nNOS-eNOS, and improved erectile function
Ryu *et al* [46]	12-wk-old C57BL/6J mice; *n* = 6 in each group (control, diabetic, diabetic with PBS, and diabetic with BMSCs)	Streptozotocin-induced diabetic mouse	Not clear	BMSCs; Allogenic	Tibiae and Femur	Yes, flow cytometry (CD3, CD44, CD45, CD103, CD105, CD117, MHC-1, and Sca-1)	3×10^5/IC	None	2 wk	e-NOS-nNOS, endothelial and smooth muscle content histology	BMSCs improved significant recovery of erectile tissue
Zhou *et al* [48]	8-wk-old male Sprague-Dawley; *n* = 5 in each group (negative control, ASCs + ad-luc-myocardin, ASCs + ad-luc, ED without treatment)	Streptozotocin-induced diabetic mouse	Not clear	ADSCs; Autologous	Paratesticular fat tissue	Not clear	1×10^6 ADSC/IC	Insulin and neutral protamine hagedorn	4 wk	ICP-MAP, AGEs, and RAGE; growth factors and cytokine in penis	ADSCs combined with insulin improved erectile function and pathological changes
Wang *et al*[52]	10-wk-old male Sprague-Dawley rats; *n* = 14-15 in each group (negative control, icariin, ADMSCs, ADMSCs + icariin)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs; Allogenic	Inguinal adipose	Yes, fluorescent-activated cell sorting (CD90, CD29, CD34, CD45)	1×10^6/IC	Icariin	4 wk	ICP-MAP, histology and immunohistology of penis tissue, intracellular ROS levels	Icariin-enhanced ADSCs in erectile function Icariin could protect ADSCs against oxidative stress
Zhou *et al* [50]	8-wk-old male Sprague-Dawley rats; (*n* = 8 in control, *n* = 20 in treated groups)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs; Allogenic	Paratesticular fat tissue	Not clear	1×10^6 ADSC and 1×10^4 ADSCs per MT/IC	Microtissues (MTs)	4 wk	ICP-MAP, nNOS, smooth and endothelial content histology	MTs improved histopathology and erectile function rather than traditional ADSC
Zhu *et al* [49]	10-wk-old male Sprague-Dawley rats; *n* = 8-10 in each group (non-diabetic controls, diabetic with PBS, ADSCs, ADSCs + Magnetic application	Streptozotocin-induced diabetic mouse	Not clear	ADSCs; Autologous	Paratesticular fat tissue	Yes, by flow cytometry (CD34, CD45, CD44)	1×10^6 ADSC	Magnetic iron oxide nanoparticle	4 wk	ICP-MAP, contents, smooth muscle (α-SMA), endothelium (von Willebrand factor), VEGF	ADSCs improved erectile function External magnetic field improved efficiency of labeled ADSC in the corpus cavernosum
Jeon *et al* [56]	8-wk-old male Sprague-Dawley rats; *n* = 12 in each group (control, DM ED, BM-MSC, SDF-1 (stromal	Streptozotocin-induced diabetic with ED	Not clear	BMSCs	Not mentioned	Not mentioned	1×10^6/IC	SDF-1	4 wk	ICP-MAP, nNOS-eNOS, FGF-VEGF *in vivo*	SDF-1 improved ED recovery and smooth muscle content, increased nNOS-eNOS, FGF-VEGF

	cell-derived factor-1)										
Chen *et al* [42]	Male Sprague-Dawley rats with unspecific age; n = 10 in each group (ADSC, BMSC, and control)	ED in type 2 rats with diabetes induced by high-fat and high-sugar diet and streptozotocin	Yes, by APO procedure	ADSCs and BMSCs; Allogenic	Medullary cavity of femur, tibia, and fibula	Yes, by flow cytometry Identification with CD34,CD45,CD73,CD90, and CD105	1×10^6/IC	None	2 wk	ICP-MAP, number of blood vessels, collagen	Stem cell improved ICP-MAP, increased the number of blood vessels, and reduced collagen content
Ouyang *et al*[72]	Male Sprague-Dawley rats with unspecific age; n = 8 in each group (control and treatment)	Streptozotocin-induced diabetes	Yes, APO procedure	HUDSCs	Human urine	Yes, flow cytometry and Western blot (CD63 and protein calnexin)	Not mentioned	None	4 wk	ICP-MAP, eNOA, phospho-eNOS, nNOS, and endothelial markers (CD31)	Human-derived stem cells improved ICP, eNOS, nNOS, and endothelial markers
Zhang *et al*[51]	Male Sprague-Dawley rats; n = 10 in each group (negative control, ASCs + ad-luc-myocardin, ASCs + ad-luc, ED without treatment)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs; Allogenic	Inguinal fat tissue	Yes, flow cytometry (CD29, CD90, CD34, and CD45)	1×10^6/IC	Ad-luc-myocardin modified	3 wk	ICP-MAP, collagen and smooth muscle histology: myocardin, collagen 1, cleaved caspase 3, α-SMA, and calponin	Myocardin enhanced therapeutic for ASCs for ED in diabetic mouse
Zhang *et al*[58]	CCECs culture, not specific rats; n = 15 each group (case and control)	CCECs treated with advanced glycation end products and streptozotocin-induced diabetic mouse	*In vivo* CCECs mimicking diabetic and APO procedure	HUDSCs	Human urine	Yes, by flow cytometry (CD24, CD31, CD34, CD44, CD45, CD73, CD90, CD105)	Not mentioned	None	4 wk	ICP-MAP, eNOS, p-NOS, VEGFRA, VEGFR2, authophagic flux	Urine stem cell improved cavernosal endothelium through upregulated authophagic activity
Zhang *et al*[47]	8-wk-old male Sprague-Dawley rats; n = 9 in each group (control group, DM with ED, ADSCs, ADSCs-EFGP, ADSCs + iNOS)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs; Allogenic	Inguinal fat tissues	Yes, by flow cytometry (CD2, CD31, CD49, CD90, CD106, CD34, CD45, CD73)	5×10^5/IC	EFGP and iNOS	2 wk	ICP-MAP, endothelial and smooth muscle content marker (NO, collagen-I, collagen IV, TGF-β, β- actin)	ADSCS-iNOS significantly reduced penile fibrosis
Song *et al* [54]	Male Sprague-Dawley rats; n = 7-8 in each group (BMSC-EXO, ADSC-EXO, CCSMC-EXO, control)	Streptozotocin-induced diabetic mouse	Yes, APO procedure	ADSCs and BMSCs; Allogenic	Inguinal adipose and rat femoral	Yes, flow cytometry (CD29, CD34, CD45, and CD90	100 μg of exosome/IC	Exosome CCSMC	4 wk	ICP-MAP, α-SMA collagen, TGF-β1, β-actin, e-NOS, and n-NOS, NO, and cGMP	CCSMC-EXOs improve erectile function, reducing collagen deposition and expression of eNOS-nNOS, NO, and cGMP
Wang *et al*[53]	Male Sprague-Dawley rats with unspecified age; no data on n number, four experimental groups in total (negative control, DM, DM +	Streptozotocin-induced diabetic mouse	Yes, but not mention what method	ADSCs; Allogenic	Not Mention	Yes, CD29, CD90, CD44, CD105, and von Willebrand factor	100 μL of exosome from ADSCs/IV	siCorin ADSC-EXO	2 wk	ICP-MAP, neurovascular function (ANP, BNP, nNOS, cGMP, β-actin) , inflammatory factor (IL6, IL1β), expression, delivery of corin	ADSC-EXO enhanced endothelial recovery and decreased inflammatory process

	ADSC-EXO, DM + siCorin-ADSC-EXO)												

APO: Apomorphine; ADSCs: Adipose-derived stem cells; BMSCs: Bone marrow stem cells; CCECs: Cavernosal vascular endothelial cells; CCSMC: Corpus cavernosal smooth muscle cell; DM: Diabetes mellitus; ED: Erectile dysfunction; HUDSCs: Human urine-derived stem cells; IC: Intracavernosal; ICP-MAP: Intracavernosal pressure-mean arterial pressure; MSCs: Muscle-derived stem cells; PMSCs: Placental matrix stem cells.

Table 2 List of articles on stem cell therapy in humans with diabetic erectile dysfunction

Ref.	Study subject and n number	Type of ED	Evidence of previous DE	Type of stem cell	Source of stem cell	Stem cell characterization	Number of cells injected and site of injection	Modification	Duration of follow-up	Parameter of therapy	Conclusion
Bahk *et al* [61]	Impotent diabetic type 2 patients range from 57 yr to 87 yr; *n* = 7 in treated groups, *n* = 3 in controls.	Diabetic ED	Yes, by clinical diagnosis and other parameters	UCBSCs; Allogenic	Umbilical cord	Yes, by flow cytometry (CD13, CD14, CD34, CD31, CD45, CD44, CD49e, CD54, CD90, CD106, and HLA-DR)	1.5×10^7/IC	None	9 mo	IIEF-5, SEP, GAQ, erection diary, blood glucose diary	Umbilical cord blood stem cell had positive effects on ED
Levy *et al* [59]	Men aged 40-70 yr who had organic ED at least 6 mo; *n* = 8	Diabetic ED	Yes, by clinical diagnosis and other parameters	PM-MSCs; Allogenic	Placenta	Not clear	1 mL PM-MSCs /IC	None	6 wk, 3 mo, 6 mo	Peak systolic velocity, end-diastolic velocity, stretched penile length, penile width, IIEF-5	The treatment may be beneficial
Al demour *et al*[60]	Men aged 25-65 yr who had ED at least 6 mo; *n* = 4	Diabetic ED	Yes, by clinical diagnosis and other parameters	BMSCs; Autologous	Iliac crest	Yes, positive for CD90, CD105, CD73, and CD44	15×10^6/IC	None	2 yr	IIEF-5, EHS	Stem cell effective and improved erectile function
Protogerou *et al*[62]	Male with ED due to DM, hypertension, hypercholesterolemia, and Peyronie's disease; *n* = 5 in each group (control and ADSC treated)	Diabetic ED	Yes, by clinical diagnosis	ADSCs; Autologous	Not mentioned	Yes, alizarin red S and alcian blue staining, flow cytometry	2×10^5/IC	None	3 mo	IIEF-5, penile triplex	No difference in IIEF-5 between the case and control group, but significant between before and after treatment in both groups

ADSCs: Adipose-derived stem cells; BMSCs: Bone marrow stem cells; ED: Erectile dysfunction; GAQ: Global assessment questions; IIEF-5: International index of erectile function; PMSCs: Placental matrix stem cells; SEP: Sexual encounter profile; UCBSCs: Umbilical cord blood stem cells.

All of the studies have reported that stem cells provide improvements of the erectile function both functionally and structurally in various animal models. As eNOS and nNOS play a major role in penile erection, these two factors are used as parameters in stem cell studies. Nearly all studies have reported improved levels of these two factors. This indicates that stem cells improve endothelial function at the molecular level.

Moreover, factors, such as VEGF, FGF, and von Willebrand factor, are believed to be vital in the improvement of ED in these studies. The increase of these factors suggests an induction of angiogenesis in the penile tissue. Furthermore, stem cells are also reported to reduce the fibrotic process in penile erectile tissue as well as modulate autophagy process[58]. Autophagy was reported to increase following stem cell treatment, which is believed to be a sign of tissue recovery and regeneration. All of these findings indicate that stem cells play a role in cell regeneration and recovery by increasing the levels of growth factors and suppressing inflammatory factors. Addition of specific factors may further improve tissue repair and erectile function compared to the administration of stem cells alone.

So far, only four studies have focused on stem cell therapy for ED in humans. Levy *et al*[59] have reported the administration of PM-SCs (placental matrix stem cells) in eight people with ED. After 6 mo following treatment, Levy *et al*[59] concluded that stem cell therapy improves erectile function. Another study by Al Demour *et al*[60] reported that the administration of bone marrow stem cells to people with ED resulted in the improvement of both the IIEF-5 and EHS scores; they further claimed that stem cell administration in the context of ED was well tolerated and safe for humans. However, these two studies have some weaknesses, for example, the studies did not include placebo control, were not randomized or blinded, and had a very small number of samples[60].

Bahk *et al*[61] conducted a study on seven diabetic patients aged 57-87 years and compared the effects of stem cell treatment with three patients who receive treatment for ED, such as PDE5 inhibitor alone. The stem cells used were umbilical cord-derived mesenchymal stem cells with a dose of 1.5×10^7 cells administered intracorporeally. This study was followed up for 9 mo, and at the end of the study, it was found that the stem cells produced a positive effect on ED as seen in the improvement of IIEF-5, SEP, GAQ, and erectile diary[61].

Protogerou *et al*[62] reported a different approach by using autologous adipose stem cells to treat ED in five people with DM. This group was compared with five other people who received platelet lysate. The number of stem cells given was 2×10^5 cells for 3 mo. At the end of the study, no difference in IIEF-5 was observed between the treatment and the control groups. However, a significant improvement was observed before and after treatment in both groups[62].

Possible mechanisms of stem cell therapy for diabetic ED

There are at least two possible mechanisms underlying the therapeutic effects of stem cell implantation for diabetic ED. First, stem cells may differentiate to specific cells and hence, regenerate the damaged tissue. In diabetic ED, the implanted stem cells may differentiate to myogenic cell precursor that subsequently in the presence of growth factors such as FGF and TGF-Beta can differentiate to myoblasts[40,63]. The myoblastic cells are known to have the capability to differentiate to vascular smooth muscle cells. The new smooth muscle cells may repair and improve damaged vascular tissues and hence improve the erectile function[64,65].

Second possible mechanism may involve the capability of stem cells to secrete beneficial paracrine factors. Stem cells are known to secrete angiogenic factors such as VEGF, basis fibroblast growth factor and SDF-1. These factors are potent inducers of angiogenesis and neovascularization[66,67]. Stem cells can also produce factors such as Wnt4 and Wnt7b, which are able to promote the differentiation of myoblasts to smooth muscle cells[63]. Together, the ability of stem cells to differentiate to smooth muscle cells and to produce beneficial paracrine factors that induce angiogenesis and neo-vascularization may be the underlying mechanisms of the therapeutic effects for diabetic ED.

CONCLUSION

Overall, based on the published data, it seems that stem cell therapy can become an alternative approach for the treatment of diabetic ED in the future. Stem cells can promote recovery and regeneration of the penile tissue following damage due to inflammation and free radicals. Studies reviewed in this paper, which are almost entirely conducted on experimental animals, certainly require further follow-up research. Information on stem cell research for ED treatment remains to be limited, but it can form the basis to develop further research in this area. In particular, larger human studies with appropriate research designs are needed to provide more objective information on the possibility of translational application.

REFERENCES

1 **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]

2 **De Berardis G**, Franciosi M, Belfiglio M, Di Nardo B, Greenfield S, Kaplan SH, Pellegrini F, Sacco M, Tognoni G, Valentini M, Nicolucci A; Quality of Care and Outcomes in Type 2 Diabetes (QuED) Study Group. Erectile dysfunction and quality of life in type 2 diabetic patients: a serious problem too often overlooked. *Diabetes Care* 2002; **25**: 284-291 [PMID: 11815497 DOI: 10.2337/diacare.25.2.284]

3 **Anwar Z**, Sinha V, Mitra S, Mishra AK, Ansari MH, Bharti A, Kumar V, Nigam AK. Erectile Dysfunction: An Underestimated Presentation in Patients with Diabetes Mellitus. *Indian J Psychol Med* 2017; **39**: 600-604 [PMID: 29200555 DOI: 10.4103/0253-7176.217015]

4 **Giugliano F**, Maiorino M, Bellastella G, Gicchino M, Giugliano D, Esposito K. Determinants of erectile dysfunction in type 2 diabetes. *Int J Impot Res* 2010; **22**: 204-209 [PMID: 20147958 DOI: 10.1038/ijir.2010.1]

5 **Jumani DK**. Erectile dysfunction in diabetes mellitus: A review. *J Diabetol* 2020; **11**: 1-7 [DOI: 10.4103/jod.jod_42_18]

6 **Kamenov ZA**, Christov VG, Yankova TM. Erectile dysfunction in diabetic men is linked more to microangiopathic complications and neuropathy than to macroangiopathic disturbances. *J Mens Heal Gend* 2007; **4**: 64-73 [DOI: 10.1016/j.jmhg.2006.12.004]

7 **Musicki B**, Burnett AL. Endothelial dysfunction in diabetic erectile dysfunction. *Int J Impot Res* 2007; **19**: 129-138 [PMID: 16775612 DOI: 10.1038/sj.ijir.3901494]

8 **Musicki B**, Kramer MF, Becker RE, Burnett AL. Inactivation of phosphorylated endothelial nitric oxide synthase (Ser-1177) by O-GlcNAc in diabetes-associated erectile dysfunction. *Proc Natl Acad Sci U S A* 2005; **102**: 11870-11875 [PMID: 16085713 DOI: 10.1073/pnas.0502488102]

9 **Dimmeler S**, Zeiher AM. Endothelial cell apoptosis in angiogenesis and vessel regression. *Circ Res* 2000; **87**: 434-439 [PMID: 10988233 DOI: 10.1161/01.res.87.6.434]

10 **Papapetropoulos A**, García-Cardeña G, Madri JA, Sessa WC. Nitric oxide production contributes to the angiogenic properties of vascular endothelial growth factor in human endothelial cells. *J Clin Invest* 1997; **100**: 3131-3139 [PMID: 9399960 DOI: 10.1172/JCI119868]

11 **Sheehy AM**, Phung YT, Riemer RK, Black SM. Growth factor induction of nitric oxide synthase in rat pheochromocytoma cells. *Brain Res Mol Brain Res* 1997; **52**: 71-77 [PMID: 9450679 DOI: 10.1016/s0169-328x(97)00224-6]

12 **Lin CS**, Ho HC, Chen KC, Lin G, Nunes L, Lue TF. Intracavernosal injection of vascular endothelial growth factor induces nitric oxide synthase isoforms. *BJU Int* 2002; **89**: 955-960 [PMID: 12010247 DOI: 10.1046/j.1464-410x.2002.02792.x]

13 **Sopko NA**, Hannan JL, Bivalacqua TJ. Understanding and targeting the Rho kinase pathway in erectile dysfunction. *Nat Rev Urol* 2014; **11**: 622-628 [PMID: 25311680 DOI: 10.1038/nrurol.2014.278]

14 **Chiou WF**, Liu HK, Juan CW. Abnormal protein expression in the corpus cavernosum impairs erectile function in type 2 diabetes. *BJU Int* 2010; **105**: 674-680 [PMID: 19751257 DOI: 10.1111/j.1464-410X.2009.08852.x]

15 **Guagnini F**, Ferazzini M, Grasso M, Blanco S, Croci T. Erectile properties of the Rho-kinase inhibitor SAR407899 in diabetic animals and human isolated corpora cavernosa. *J Transl Med* 2012; **10**: 59 [PMID: 22444253 DOI: 10.1186/1479-5876-10-59]

16 **Wang H**, Eto M, Steers WD, Somlyo AP, Somlyo AV. RhoA-mediated Ca2+ sensitization in erectile function. *J Biol Chem* 2002; **277**: 30614-30621 [PMID: 12060659 DOI: 10.1074/jbc.M204262200]

17 **Clozel M**, Gray GA, Breu V, Löffler BM, Osterwalder R. The endothelin ETB receptor mediates both vasodilation and vasoconstriction in vivo. *Biochem Biophys Res Commun* 1992; **186**: 867-873 [PMID: 1323294 DOI: 10.1016/0006-291x(92)90826-7]

18 **Cartledge JJ**, Eardley I, Morrison JF. Advanced glycation end-products are responsible for the impairment of corpus cavernosal smooth muscle relaxation seen in diabetes. *BJU Int* 2001; **87**: 402-407 [PMID: 11251537 DOI: 10.1046/j.1464-410x.2001.00067.x]

19 **Nofzinger EA**. Sexual Dysfunction in Patients with Diabetes Mellitus: The Role of a "Central" Neuropathy. *Semin Clin Neuropsychiatry* 1997; **2**: 31-39 [PMID: 10320441]

20 **Yagihashi S**, Yamagishi S, Wada R. Pathology and pathogenetic mechanisms of diabetic neuropathy: correlation with clinical signs and symptoms. *Diabetes Res Clin Pract* 2007; **77** Suppl 1: S184-S189 [PMID: 17462777 DOI: 10.1016/j.diabres.2007.01.054]

21 **Ho CH**, Jaw FS, Wu CC, Chen KC, Wang CY, Hsieh JT, Yu HJ, Liu SP. The prevalence and the risk factors of testosterone deficiency in newly diagnosed and previously known type 2 diabetic men. *J Sex Med* 2015; **12**: 389-397 [PMID: 25441980 DOI: 10.1111/jsm.12777]

22 **Araujo AB**, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab* 2007; **92**: 4241-4247 [PMID: 17698901 DOI: 10.1210/jc.2007-1245]

23 **Imai A**, Yamamoto H, Hatakeyama S, Iwabuchi I, Yoneyama T, Hashimoto Y, Koie T, Kamimura N, Danjyo K, Ohyama C. Risk factors for erectile dysfunction in healthy Japanese men. *Int J Androl* 2010; **33**: 569-573 [PMID: 19708864 DOI: 10.1111/j.1365-2605.2009.00974.x]

24 **Rosen RC**, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11**: 319-326 [PMID: 10637462 DOI: 10.1038/sj.ijir.3900472]

25 **Mulhall JP**, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the erection hardness score. *J Sex Med* 2007; **4**: 1626-1634 [PMID: 17888069 DOI: 10.1111/j.1743-6109.2007.00600.x]

26 **Cho NH**, Ahn CW, Park JY, Ahn TY, Lee HW, Park TS, Kim IJ, Pomerantz K, Park C, Kimm KC, Choi DS. Prevalence of erectile dysfunction in Korean men with Type 2 diabetes mellitus. *Diabet Med* 2006; **23**: 198-203 [PMID: 16433719 DOI: 10.1111/j.1464-5491.2005.01789.x]

27 **Bacon CG**, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. A prospective study of risk factors for erectile dysfunction. *J Urol* 2006; **176**: 217-221 [PMID: 16753404 DOI: 10.1016/S0022-5347(06)00589-1]

28 **Fung MM**, Bettencourt R, Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. *J Am Coll Cardiol* 2004; **43**: 1405-1411 [PMID: 15093875 DOI: 10.1016/j.jacc.2003.11.041]

29 **Cheng JY**, Ng EM, Chen RY, Ko JS. Alcohol consumption and erectile dysfunction: meta-analysis of population-based studies. *Int J Impot Res* 2007; **19**: 343-352 [PMID: 17538641 DOI: 10.1038/sj.ijir.3901556]

30 **Glina S**, Virag R, Luis Rhoden E, Sharlip ID. Intracavernous injection of papaverine for erectile failure R. Virag. *J Sex Med* 2010; **7**: 1331-1335 [DOI: 10.1111/j.1743-6109.2010.01774.x]

31 **Belew D**, Klaassen Z, Lewis RW. Intracavernosal Injection for the Diagnosis, Evaluation, and Treatment of Erectile Dysfunction: A Review. *Sex Med Rev* 2015; **3**: 11-23 [PMID: 27784568 DOI: 10.1002/smrj.35]

32 **Yuan J**, Hoang AN, Romero CA, Lin H, Dai Y, Wang R. Vacuum therapy in erectile dysfunction--science and clinical evidence. *Int J Impot Res* 2010; **22**: 211-219 [PMID: 20410903 DOI: 10.1038/ijir.2010.4]

33 **Price DE**, Cooksey G, Jehu D, Bentley S, Hearnshaw JR, Osborn DE. The management of impotence in diabetic men by vacuum tumescence therapy. *Diabet Med* 1991; **8**: 964-967 [PMID: 1838050 DOI: 10.1111/j.1464-5491.1991.tb01538.x]

34 **Phé V**, Rouprêt M. Erectile dysfunction and diabetes: a review of the current evidence-based medicine and a synthesis of the main available therapies. *Diabetes Metab* 2012; **38**: 1-13 [PMID: 22056307 DOI: 10.1016/j.diabet.2011.09.003]

35 **Mokry J**, Pisal R. The basic principles of stem cells. *Stem Cell Biol Tissue Eng Dent Sci* 2015; 237-248 [DOI: 10.1016/B978-0-12-397157-9.00019-9]

36 **Ragab El Barky A**, Ali EMM, Mohamed TM. Stem Cells, Classifications and their Clinical Applications. *Am J Pharmacol Ther* 2017; **1**: 1-7

37 **Donnelly H**, Salmeron-Sanchez M, Dalby MJ. Designing stem cell niches for differentiation and self-renewal. *J R Soc Interface* 2018; **15** [PMID: 30158185 DOI: 10.1098/rsif.2018.0388]

38 **Dai R**, Wang Z, Samanipour R, Koo KI, Kim K. Adipose-Derived Stem Cells for Tissue Engineering and Regenerative Medicine Applications. *Stem Cells Int* 2016; **2016**: 6737345 [PMID: 27057174 DOI: 10.1155/2016/6737345]

39 **Mercado C**. Adipose-derived adult stem cells and new technique for intracavernosal injection for erectile dysfunction: Novel approach to treat diabetes mellitus. Erectus Shot Technique. *Integr Mol Med* 2016; **3**: 564-575 [DOI: 10.15761/IMM.1000206]

40 **Chung E**. Stem-cell-based therapy in the field of urology: a review of stem cell basic science, clinical applications and future directions in the treatment of various sexual and urinary conditions. *Expert Opin Biol Ther* 2015; **15**: 1623-1632 [PMID: 26243575 DOI: 10.1517/14712598.2015.1075504]

41 **He M**, von Schwarz ER. Stem-cell therapy for erectile dysfunction: a review of clinical outcomes. *Int J Impot Res* 2021; **33**: 271-277 [PMID: 32350455 DOI: 10.1038/s41443-020-0279-8]

42 **Chen S**, Zhu J, Wang M, Huang Y, Qiu Z, Li J, Chen X, Chen H, Xu M, Liu J, She M, Li H, Yang X, Wang Y, Cai X. Comparison of the therapeutic effects of adiposederived and bone marrow mesenchymal stem cells on erectile dysfunction in diabetic rats. *Int J Mol Med* 2019; **44**: 1006-1014 [PMID: 31257465 DOI: 10.3892/ijmm.2019.4254]

43 **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]

44 **Lipshultz LI**, Pastuszak AW, Goldstein AT, Giraldi A, Perelman MA. Management of sexual dysfunction in men and women: An interdisciplinary approach. *Manag Sex Dysf Men Women Interdisc Appr* 2016; 1-396

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 **Ryu JK**, Kim DH, Song KM, Ryu DS, Kim SN, Shin DH, Yi T, Suh JK, Song SU. Intracavernous delivery of clonal mesenchymal stem cells rescues erectile function in the streptozotocin-induced diabetic mouse. *Andrology* 2016; **4**: 172-184 [PMID: 26711324 DOI: 10.1111/andr.12138]

47 **Zhang Y**, Yang J, Zhuan L, Zang G, Wang T, Liu J. Transplantation of adipose-derived stem cells overexpressing inducible nitric oxide synthase ameliorates diabetes mellitus-induced erectile dysfunction in rats. *PeerJ* 2019; **7**: e7507 [PMID: 31423366 DOI: 10.7717/peerj.7507]

48 **Zhou F**, Hui Y, Xu Y, Lei H, Yang B, Guan R, Gao Z, Xin Z, Hou J. Effects of adipose-derived stem cells plus insulin on erectile function in streptozotocin-induced diabetic rats. *Int Urol Nephrol* 2016; **48**: 657-669 [PMID: 26820518 DOI: 10.1007/s11255-016-1221-3]

49 **Zhu LL**, Zhang Z, Jiang HS, Chen H, Chen Y, Dai YT. Superparamagnetic iron oxide nanoparticle targeting of adipose tissue-derived stem cells in diabetes-associated erectile dysfunction. *Asian J Androl* 2017; **19**: 425-432 [PMID: 27157506 DOI: 10.4103/1008-682X.179532]

50 **Zhou F**, Hui Y, Xin H, Xu YD, Lei HE, Yang BC, Guan RL, Li M, Hou JQ, Xin ZC. Therapeutic effects of adipose-derived stem cells-based microtissues on erectile dysfunction in streptozotocin-induced diabetic rats. *Asian J Androl* 2017; **19**: 91-97 [PMID: 27345005 DOI: 10.4103/1008-682X.182817]

51 **Zhang HB**, Chen FZ, He SH, Liang YB, Wang ZQ, Wang L, Chen ZR, Ding W, Zhao SC, Wei AY. In vivo tracking on longer retention of transplanted myocardin gene-modified adipose-derived stem cells to improve erectile dysfunction in diabetic rats. *Stem Cell Res Ther* 2019; **10**: 208 [PMID: 31311594 DOI: 10.1186/s13287-019-1325-7]

52 **Wang X**, Liu C, Xu Y, Chen P, Shen Y, Zhao Y, Chen W, Zhang X, Ouyang Y, Wang Y, Xie C, Zhou M. Combination of mesenchymal stem cell injection with icariin for the treatment of diabetes-associated erectile dysfunction. *PLoS One* 2017; **12**: e0174145 [PMID: 28350842 DOI: 10.1371/journal.pone.0174145]

53 **Wang J**, Mi Y, Wu S, You X, Huang Y, Zhu J, Zhu L. Exosomes from adipose-derived stem cells protect against high glucose-induced erectile dysfunction by delivery of corin in a streptozotocin-induced diabetic rat model. *Regen Ther* 2020; **14**: 227-233 [PMID: 32435675 DOI: 10.1016/j.reth.2020.03.002]

54 **Song J**, Sun T, Tang Z, Ruan Y, Liu K, Rao K, Lan R, Wang S, Wang T, Liu J. Exosomes derived from smooth muscle cells ameliorate diabetes-induced erectile dysfunction by inhibiting fibrosis and modulating the NO/cGMP pathway. *J Cell Mol Med* 2020; **24**: 13289-13302 [PMID: 33009701 DOI: 10.1111/jcmm.15946]

55 **Ouyang B**, Sun X, Han D, Chen S, Yao B, Gao Y, Bian J, Huang Y, Zhang Y, Wan Z, Yang B, Xiao H, Songyang Z, Liu G, Deng C. Human urine-derived stem cells alone or genetically-modified with FGF2 Improve type 2 diabetic erectile dysfunction in a rat model. *PLoS One* 2014; **9**: e92825 [PMID: 24663037 DOI: 10.1371/journal.pone.0092825]

56 **Jeon SH**, Zhu GQ, Bae WJ, Choi SW, Jeong HC, Cho HJ, Ha US, Hong SH, Lee JY, Kwon EB, Kim HJ, Lee SM, Kim HY, Kim SW. Engineered Mesenchymal Stem Cells Expressing Stromal Cell-derived Factor-1 Improve Erectile Dysfunction in Streptozotocin-Induced Diabetic Rats. *Int J Mol Sci* 2018; **19** [PMID: 30477146 DOI: 10.3390/ijms19123730]

57 **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]

58 **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]

59 **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]

60 **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]

61 **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]

62 **Protogerou V**, Michalopoulos E, Mallis P, Gontika I, Dimou Z, Liakouras C, Stavropoulos-Giokas C, Kostakopoulos N, Chrisofos M, Deliveliotis C. Administration of Adipose Derived Mesenchymal Stem Cells and Platelet Lysate in Erectile Dysfunction: A Single Center Pilot Study. *Bioengineering (Basel)* 2019; **6** [PMID: 30841525 DOI: 10.3390/bioengineering6010021]

63 **Ferraris VA**. How do cells talk to each other? *J Thorac Cardiovasc Surg* 2016; **151**: 849-851 [PMID: 26707722 DOI: 10.1016/j.jtcvs.2015.11.035]

64 **Placzek MR**, Chung IM, Macedo HM, Ismail S, Mortera Blanco T, Lim M, Cha JM, Fauzi I, Kang Y, Yeo DC, Ma CY, Polak JM, Panoskaltsis N, Mantalaris A. Stem cell bioprocessing: fundamentals and principles. *J R Soc Interface* 2009; **6**: 209-232 [PMID: 19033137 DOI: 10.1098/rsif.2008.0442]

65 **Protogerou V**, Chrysikos D, Karampelias V, Spanidis Y, Sara EB, Troupis T. Erectile Dysfunction Treatment Using Stem Cells: A Review. *Medicines (Basel)* 2021; **8** [PMID: 33419152 DOI: 10.3390/medicines8010002]

66 **Soker S**, Machado M, Atala A. Systems for therapeutic angiogenesis in tissue engineering. *World J*

Urol 2000; **18**: 10-18 [PMID: 10766038 DOI: 10.1007/pl00007070]

67 **Cahill TJ**, Choudhury RP, Riley PR. Heart regeneration and repair after myocardial infarction: translational opportunities for novel therapeutics. *Nat Rev Drug Discov* 2017; **16**: 699-717 [PMID: 28729726 DOI: 10.1038/nrd.2017.106]

68 **Garcia MM**, Fandel TM, Lin G, Shindel AW, Banie L, Lin CS, Lue TF. Treatment of erectile dysfunction in the obese type 2 diabetic ZDF rat with adipose tissue-derived stem cells. *J Sex Med* 2010; **7**: 89-98 [PMID: 20104670 DOI: 10.1111/j.1743-6109.2009.01541.x]

69 **Li Y**, Pan E, Wang Y, Zhu X, Wei A. Flk-1^+Sca-1^- mesenchymal stem cells: functional characteristics *in vitro* and regenerative capacity in vivo. *Int J Clin Exp Pathol* 2015; **8**: 9875-9888 [PMID: 26617697]

70 **Wang X**, Liu C, Li S, Xu Y, Chen P, Liu Y, Ding Q, Wahafu W, Hong B, Yang M. Hypoxia precondition promotes adipose-derived mesenchymal stem cells based repair of diabetic erectile dysfunction *via* augmenting angiogenesis and neuroprotection. *PLoS One* 2015; **10**: e0118951 [PMID: 25790284 DOI: 10.1371/journal.pone.0118951]

71 **Kovanecz I**, Vernet D, Masouminia M, Gelfand R, Loni L, Aboagye J, Tsao J, Rajfer J, Gonzalez-Cadavid NF. Implanted Muscle-Derived Stem Cells Ameliorate Erectile Dysfunction in a Rat Model of Type 2 Diabetes, but Their Repair Capacity Is Impaired by Their Prior Exposure to the Diabetic Milieu. *J Sex Med* 2016; **13**: 786-797 [PMID: 27114192 DOI: 10.1016/j.jsxm.2016.02.168]

72 **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]

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