Prospective Study

Potential therapeutic applications of mesenchymal stem cells for erectile dysfunction in diabetes mellitus: From preclinical/clinical perspectives

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Abstract

Diabetes-related complications affect all body organ systems, including the penis. Diabetes-induced erectile dysfunction (ED) is caused by neuropathy of the penile nerves and vasculopathy of the smooth muscle and endothelium corpus cavernosum. To present an overview of Mesenchymal Stem Cell (MSC) research in diabetic animal models of ED, focusing on the function, signaling, and niches that have a prominent role in the regeneration of cavernosal cells and restoration of penile tissues. We highlight common erectile pathologies caused by diabetes and review relevant preclinical trials. We also discuss paracrine mechanisms of various MSC therapies involved in the repair of endothelial cells and cavernous nerves in these diabetic models. A PubMed search was performed, with dates ranging from inception until November 20, 2019. This review provides a comprehensive evaluation of the various strategies that have been investigated for improving MSC delivery methods, through preclinical literature and published clinical trials regarding ED in men with diabetes. MSC-type applications have been beneficial to erectile function in diabetic models of ED. This review examines the progress and remaining challenges in diabetes-related SC research regarding ED. Moving forward, it is only with a combined effort of basic biology and translational work that the potential of MSC-based therapies in diabetes can be realized.

Introduction

Diabetes mellitus affects millions of people globally, and its complications can be harmful to all body systems[1,2]. Diabetic men exhibit a higher prevalence of erectile dysfunction (ED) than non-diabetic men[3-5], with epidemiological studies documenting that up to 75% of diabetic men suffer from ED [6,7].

Diabetic ED involves nerve damage, endothelial injury, and cavernosal muscle fibrotic alterations (Figure 1) [3,8-10]. Complications due to diabetes can limit blood flow into the penis if atherosclerotic damage corresponds to major blood vessels in the vascular system [11]. Advanced glycation endproducts (AGE) cause microvascular complications as pathogenesis of ED in streptozotocin-induced diabetic rats[12]. AGE and its receptor (RAGE) interaction develop a metabolic memory [13-15]. Insulin therapy for glycemic control can reduce AGE and RAGE and control the corresponding inflammatory response in the penis[14,16].

Diabetic ED is currently managed by Phosphodiesterase (PDE)–5 inhibitors, vacuum erection devices, and prosthetic surgery. Though they are considered first-line ED treatments, the efficacy of oral PDE–5 inhibitor treatments, such as tadalafil, vardenafil, sildenafil, and avanafil, is lower in diabetic men compared with nondiabetic men, as these treatments do not alter the existing pathological changes caused by diabetes[17]. The effectiveness of PDE–5 inhibitors is further reduced due to inadequate nitric oxide (NO) bioavailability from both
Integrity is critically important for normal erectile physiology. Both locations of the cavernous nerve [26,27] contain nNOS nitrergic nerve of the rat branches into the dorsal and intracavernous nerves. There is a loss of nNOS nitrergic nerve involved in a normal erection [23,25]. For instance, the main cavernous NO synthase [24] and neuronal (n) NOS and plays a crucial role in the formation by an enzymatic pathway involving both endothelial, nerve, and smooth muscle cells [22,23]. NO is formed by an enzymatic pathway involving both endothelial, nerve, and smooth muscle cells [22,23]. NO is involved in the formation of cGMP pathway is severely affected by diabetic ED men.

The past decade has witnessed no significant developments in treatment options for men with diabetes-related ED; however, there has been considerable attention given to preclinical studies centered on stem cell therapies for ED in diabetic men [20]. Recent efforts to treat ED at a preclinical level have consisted of isolating SCs from various organs, such as bone marrow, adipose tissue, and human umbilical cord blood [20,21]. This review focuses on the advances of various mesenchymal stem cell (MSC) delivery methods, through preclinical literature and published clinical trials regarding ED in men with diabetes.

Penile erection and diabetic ED

Erectile function is a multifaceted neurovascular phenomenon that necessitates the healthy coordination of endothelial, nerve, and smooth muscle cells [22,23]. NO is formed by an enzymatic pathway involving both endothelial NO synthase [24] and neuronal (n) NOS and plays a crucial role in a normal erection [23,25]. For instance, the main cavernous nerve of the rat branches into the dorsal and intracavernous nerves. There is a loss of nNOS nitrergic fibers due to damage to both locations of the cavernous nerve [26,27]. Cavernous nerve integrity is critically important for normal erectile physiology.

Burke, et al. [28] documented that nearly 50% of diabetic men aged 40–79 years suffer from ED. Additionally, many men seeking help for their ED are unaware they have diabetes [8]; however, clinical studies demonstrate that early metabolic control may delay the onset of diabetic complications. The analysis of both semen testosterone levels and hemoglobin Ac is a vital part of the clinical evaluation and treatment of diabetes, as diabetic men with sexual disorders have elevated glycated-hemoglobin levels (>6.5%) (Figure 1) [29]. Angulo, et al. [30] described that the NO-cyclic guanosine monophosphate (cGMP) pathway is severely affected by diabetic ED men.

Physiological loss of the properties of the endothelium leads to vascular endothelial dysfunction and a shift to a prothrombotic, vasoconstrictor, and proinflammatory state. This status is considered to be the initial insult in the progression of diabetic ED [31]. The smooth muscle relaxation by NO–mediated neurotransmission is reduced, and vascular hemodynamics in penile tissue is altered by chronic hyperglycemia [23,32]. Severe diabetes decreases NO bioavailability as a result of damage to the nitrergic nerves that serve the penile Corpus Cavernosum (CC). Furthermore, the effect of vasoconstrictor mediators, including endothelin-1 and angiotensin II, is increased in diabetes [23,33,34]. The tight control of glycemia is an essential first step in the management of diabetes-related ED. In a recent study of ED in a rat model of type 1 diabetes, islet transplantation with improved hyperglycemic status allowed for smooth muscle cell regeneration, and reduced CC fibrosis to its normal state in rats.

Figure 1: Evolution of translational MSC regenerative therapies in erectile dysfunction in diabetes. Paracrine effects can positively influence many processes, among them neural survival and neovascularization. True diabetic erectile regeneration with stem-cell treatment will require careful consideration at each step, from the isolation of the cells to their stable and safe long-term integration.

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with advanced-stage diabetes [35]. Hyperglycemia-induced tissue damage occurs via increased levels of oxygen-free radicals [36,37]. The underlying mechanism in the restoration of CC fibrosis by islet transplantation may be due to inhibition of transforming growth factor (TGF-β1/Samd2/ connective tissue growth factor) in a rat model of type 1 diabetes [35]. Diabetic microvascular complications are associated with AGE in the ED pathogenesis in streptozotocin-induced diabetic rats [12].

Type-2 diabetic patients have a higher incidence of hypogonadism and ED [38]. Erectile function and sexual desire in type-2 diabetic men can be improved by testosterone replacement therapy (TRT). However, available data are inadequate, and the long-standing benefits of TRT are not well described in this diabetic population. TRT may be offered to type-2 diabetic men after all potential risks and benefits of treatment have been discussed [39].

In earlier studies using animal models of ED, SC treatment prevented neuronal and endothelial dysfunction in the penises of diabetic rats [40]. Erectile function was restored by bone marrow–derived SCs (BMSCs) and adipose–derived SCs (ADSCs), with increased generation of penile endothelial, smooth muscle, and neuronal cells [41–43]. nNOS and eNOS expressions in the cavernous tissues were increased by SCs in a diabetic rat model. Angulo, et al. [39] described that the NO–cyclic guanosine monophosphate (cGMP) pathway is severely affected by diabetic ED men. Also, various types of cytokines, such as brain–derived neurotrophic factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) are increased, and cavernous tissues are protected from apoptosis with the promotion of cell survival [44]. Intracavernous BMSCs differentiate into cells expressing both endothelial and smooth muscle markers. In the case of diabetes, numerous studies have reported that intracavernous–transplanted mesenchymal stem cells (MSCs) regenerate endothelial and smooth muscle cells in the CC of diabetic rats [45,46].

**A challenge in the management of diabetic ED**

The first-line treatment for ED is oral PDE-5 inhibitors, which are well recognized as less clinically useful in diabetic ED. While approximately 35% of patients with ED will fail to respond to PDE5 inhibitors, in diabetic men the figure is 70%. The inadequate response to these agents stems from cGMP levels not reaching the threshold needed to induce a penile erection. This is due to insufficient NO caused by severe endothelial dysfunction and neuropathy. These agents generally inhibit GMP breakdown and augment the NO–cGMP pathway [30,47]. Combination therapy for diabetic ED involves PDE-5 inhibitors and TRT. Several antioxidants (e.g., ascorbic acid, melatonin, vitamin E, and sodium selenite) have been documented to partially restore ED in experimental diabetic animal models [36].

**MSCs**

MSCs are easily isolated from bone marrow and adipose tissue (BMSCs and ADSCs). The hypoimmunogenicity and immunomodulatory effects of MSCs have been well characterized and they have been widely used in clinical practice [48]. MSCs show both transdifferentiation capability and self-renewal potential and can be expanded in vitro, and then directed to various cell lineages to differentiate into cell types such as endothelial, smooth muscle, neuronal, and Schwann cells [49,50]. MSCs also secrete cytokines and paracrine factors that may enhance cell survival and angiogenesis and induce anti-apoptotic, pro-neurogenic, anti-inflammatory, and anti-fibrotic effects [51,52].

The pore-forming "large potassium conductance calcium-activated channel" proteins of cell membranes are encoded by the gene KCNMA1 (potassium large-conductance calcium-activated channel) [23,53]. In an earlier study, KCNMA1-transfected BMSCs improved erectile function in diabetic rats [54]. Hyperpolarization of the membrane decreased the excitability of cells, and functional ion channel-mediated intracellular K+ outflow was increased by its expression [55].

Bahk et al. reported that penile blood flow and erectile function were improved by chronic placental matrix–derived MSC injections for ED in type-2 diabetic patients [23,56]. Although not all of the patients had satisfactory erections without oral medications or injectables, none of them requested a penile prosthesis [23].

Diabetes–associated ED has been reported to benefit from low-energy shockwave therapy (LESWT), with the claims that nNOS positive nerves, endothelial, and smooth muscle cells in the penile tissue were regenerated by this treatment. SC transplantation combined with LESPWT may be one suitable treatment for diabetic ED [57].

The improved erectile function observed by the combination of LESPWT and BMSC in diabetic rats was more efficient than BMSC transplantation alone [23,58]. Zhu, et al. [59] suggested that the combination approach stimulated autophagy and decreased apoptosis in the diabetic rat CC. After intracavernous transplantation of BMSCs, smooth muscle and endothelial content increased, inducing normal erectile function in diabetic rats. Labeled BMSCs were observed in the penis post–injection after four weeks, caused by the secretion of neurotrophic factors [20,60,61]. Erectile function was restored with the transplantation of Flk-1(+)Sca-1(−) mesenchymal SCs(Flk-1(+)Sca-1(−) MSCs) in STZ diabetic rats [62]. Flk-1(+) Sca-1(−) MSCs were engrafted and led to homing of damaged muscle, myofibers restoration, partial reconstitution of the sarcolemmal expression of myoactin, and restored specific pathological marker levels [62].

Intracavernosal injection of clonal BMSCs in streptozotocin–induced diabetic mice significantly recovered erectile function [63]. Increased cavernosal smooth muscle and endothelial cells, penile eNOS phosphorylation (Ser1177), and nNOS and neurofilament were restored to 80–90% of the control values [23].

Recently, Bcl-2-modified BMSCs were transplanted to treat diabetic ED in a rat model of type 2 diabetes [64]. Bcl-2 contributed to the function of BMSCs and improved
intracavernosal pressure (ICP)/ mean arterial pressure (MAP) and erections in diabetic ED rats [64].

Recently, BM–MSCs with a significantly lowered maternally expressed gene (MEG)–3 were implanted intracavernous and improved ED of diabetic rats [65]. FOXM1 protein can be degraded by MEG3, and the differentiation of the endothelium is ultimately regulated by BM–MSCs [65].

A significant aspect of diabetic complications is an injury caused by oxidative stress due to hyperglycemia; therefore, future studies of the antioxidant capacity of MSCs are warranted. Endothelial–progenitor cells (EPCs) from the bone marrow can be mobilized to counter diabetes–induced oxidative stress. In 2012, Qui et al. documented that treatment with melatonin promoted EPC mobilization and thereby preserved erectile function in type-1 diabetic rats [66]. ED was improved by transplantation of VEGF165–transfected EPCs into the CC of diabetic rats [67]. In a previous study, tissue repair and angiogenesis were synergistically promoted by the combined transplantation of MSCs and EPCs [68].

There are many unanswered questions, e.g., the question of single versus multiple injections. A single injection of MSCs may be insufficient for the maintenance of a long–term therapeutic effect. Similarly, the management of potency by multiple MSC injections within a short interval and the dosage of MSC infusions need to be further explored.

Because of the complicated pathogenesis of diabetes mellitus, intrinsic dysfunction of the bone marrow SC niche ultimately results in MSC failure [23]. Some strategies for reducing the functional inability of BM–MSCs need to be recognized. HbA1c reduction and insulin requirements require close clinical follow-up to improve the efficacy of MSC treatment in type II diabetes[23]. Similarly, ED studies using a diabetic animal model need to observe changing insulin resistance when using MSC therapies. While available data from animal and human studies are encouraging, MSC therapy may signify a new paradigm for glycemic control in type-2 diabetes.

The main biocomponent of the secretome is the exosome, which is a naturally occurring membrane nanoparticle of 30–120 nm in diameter that mediates intercellular communication by delivering biomolecules into recipient cells[69,70]. Exosomes carry many molecules, including miRNAs, proteins, and lipids as a composite cargo, as well as the exosome cargo, which is transferable to different cell types. These recipient cells undergo expression and functional changes with exosome uptake [71,72]. The role of exosomes in diabetic ED needs further study.

The nanosized exosomes derived from MSCs may become a valuable therapeutic strategy in regenerative therapies compared with transplanted exogenous MSCs. There are many advantages of nanosized exosomes compared with exogenous MSCs. Exosomes are more natural to preserve and transfer, have lower immunogenicity, and are safer for therapeutic administration [73]. Exosomes derived from BMSCs may become a treatment for diabetes–induced ED. MSCs with hypoxic preconditioning may provide additional benefit in diabetes–induced ED, due to increased angiogenesis and neuroprotection [74].

Erythropoietin [75] is a potent cytokine capable of reducing apoptosis of Schwann cells. However, the expression of EPO in MSC is limited, though overexpression of EPO in MSC significantly improves neuroprotective actions. EPO–MSCs have the potential to reduce apoptosis of diabetes–triggered Schwann cells. Thus, suppression is likely due to the reduction of oxidative stress and apoptosis–related protein factors. Studies have revealed that the placenta (P)–derived MSCs have potent paracrine and differentiation potential effects in diabetic nude rats[76]. P–MSCs that survived three weeks accelerated the recovery of ischemic damage by increased generation of arterioles, the formation of capillaries, and the secretion of various proangiogenic factors [76].

MSCs combined with pioglitazone, or exendin–4 demonstrated substantial benefit compared with MSCs alone in regards to cardioprotective effects [77]. Recently, Jeon et al. [78] showed that stromal cell–derived factor–1 (SDF–1)–expressing engineered MSCs improved erectile function in STZ–induced diabetic ED rats [23]. A recent phase-1 clinical study proved the safety, tolerability, and efficiency of intracavernous autologous BM–MSC injections to treat ED in diabetic patients [79].

ADSCs

Adipose tissue is also a possible source for SCs, as ADSCs have self–renewal and multipotency characteristics similar to BMSCs [20,21]. The main advantages of ADSCs are that they are accessible to culture and easily collected from patients by a minimally invasive procedure, such as liposuction. The successful transplantation of allogeneic and xenogeneic ADSC illustrates their low immunogenicity [80,81].

Growing evidence suggests the success of ADSC in several ED models[82]. Intracavernosal unmodified ADSCs have been shown to restore erectile function in numerous rat ED models[42,83].

The preservation of neuronal and endothelial cells of CC in rat ED models has been observed after the intracavernous administration of cultured ADSCs [42,46]. Rats with diabetic ED treated with autologous ADSCs displayed improvement of erectile function, as well as reduced apoptosis of cavernous tissues, but few labeled ADSCs were identified [46]. The therapeutic benefit of ADSCs appears to be an indirect mechanism, whereby ADSCs improve the extracellular environment and local tissue function via the direct transformation of ADSCs into local cell types[46]. Intracavernosal injection of ADSC to a VEGF–treated group of ED in a rodent diabetic model demonstrated improved erectile function linked to an amplified expression of smooth muscle, endothelial, and pericyte markers[84]. The potential of ADSCs to regenerate and repair various tissues deserves more focus [85].

An ideal source for SC and stromal cells are the ADSC stromal vascular fraction (SVF). Human SVF was isolated from five patients undergoing reduction mammoplasty and...
administered to C57BL/6J mice after induction of diabetes. At eight weeks, erectile function was restored by increased endothelial and smooth muscle cells, nNOS–positive nerve fibers, and eNOS phosphorylation in diabetic mice [86].

This benefit witnessed in animal models [45,87] suggests that SC therapy may recover erectile function in humans [23]. Furthermore, the overexpression of adenomedullin by ADSC enhanced erectile function in diabetic rats, likely by amplified VE–cadherin and eNOS expressions in diabetic rats [88].

Various forms of fibrosis involve the TGFβ1–Smad signaling pathway. Hepatocyte growth factor (HGF) is known to inhibit the TGFβ1–Smad signaling pathway and attenuate renal fibrosis in diabetic rats [89,90]. Similarly, penile fibrosis occurs as a pathological response to diabetes. Erectile function was improved by ADSC monotherapy in streptozotocin–induced diabetic rats, and the benefit was augmented when combined with HGF, resulting in a higher number of endothelial and smooth muscle cells and a lower cell apoptotic index in the CC [91].

Tissue inhibitors of matrix metalloproteinase -1 (MMP–1), lipopolysaccharide–inducible CXC chemokine (LIX), and VEGF are expressed after ADSC delivery [12]. Cavernous endothelium, smooth muscle, and nNOS–positive nerves were partially preserved, and apoptosis was reduced in ADSC–treated diabetic rats [12]. Theoretically, the addition of insulin may further control the inflammatory response and decrease AGE–product accumulation in the penis [12,23,63].

In other experiments, a streptozotocin–diabetic rat, transplantation with pigment epithelium–derived factor (PEDF)–transfected ADSCs successfully improved ICP/MAP ratios as compared with untreated ADSC [92]. Overexpression of PEDF resulted in higher survival rates and decreased apoptosis of ADSC[92]. ADSC transplantation restored erectile function in a diabetic rat model by attenuating the harmful effects of hyperglycemia. Thus, the therapeutic potential of ADSC for treating ED, as well as the additional benefits of PEDF overexpression, is an exciting development [92]. At the early stages of elevated glucose levels in type–2 diabetic rats, nNOS and eNOS were unregulated and corporal veno–occlusive dysfunction (CVOD), caused by contracted smooth muscle, increased collagen, and fat infiltration was improved by SC delivery [23,93]. However, SCs administered at a later stage in this high–glucose in a streptozotocin–diabetic rat model were unsuccessful in restoring functional corporal tissue [23,92].

In a recent study, the in vivo homing efficiency provided by superparamagnetic iron oxide nanoparticles (SPION)–labeled ADSCs to the CC region was improved by the use of an external magnetic field in a rat model of diabetic ED [23,94]. Smooth muscle and endothelial density increased after magnetic field–guided SPION–labeled ADSCs in the CC, and erectile function was improved when compared to ADSC treatment alone[94]. The combination of intracavernous injection of ADSCs and icariin via daily gastric gavage augmented ICP and ICP/MAP values [23,95]. Thus, icariin has a positive effect on ADSC treatment of diabetic ED [95]. ADSC–derived exosomes also induced a beneficial effect on erectile function in a type–2 diabetic rat model [96]. Exosomes were isolated from the supernatants of cultured ADSC by ultracentrifugation. ADSC–derived exosomes, similar to ADSC, were capable of rescuing CC endothelial and smooth muscle cells by inhibiting apoptosis and thus promoting the recovery of erectile function in a type–2 diabetic rat model (using a high–fat diet and low–dose streptozotocin administered by intraperitoneal injection) [64]. ADSCs–based Microtissues (MT) in STZ–induced diabetic rats with ED induced expression of Nerve Growth Factor (NGF), VEGF, and tumor necrosis factor–stimulated gene–6 [97]. Also, MT treatment improved ICP, nNOS levels, and endothelial and smooth muscle contents and reduced local inflammation in the CC of diabetic rats. MTs combined with intracavernosal ADSC enhanced erectile function and histopathological changes in streptozotocin–induced diabetic rats [97]. Very recently, the injection of ADSCs into the tunica albuginea during the active phase of Peyronie’s disease prevents the development of fibrosis [98].

ADSCs and platelet–rich plasma co–transplantation is an attractive option in therapies using autologous cells. However, transplantation of ADSCs is often exposed to hostile environments in which local oxidative stress, hypoxia, and inflammation induce early cell loss. Reduced survival of transplanted ADSCs will dramatically reduce their therapeutic effects. Of note, a current study in a rat model of type 2 diabetes showed that hypoxia–preconditioning promoted ADSC–based repair of diabetes–induced ED by augmenting angiogenesis and neuroprotection [99].

The efficacy of ADSC in improving ED in diabetic rats is mainly derived through a paracrine effect. ADSC–derived exosomes, similar to ADSC, are capable of restoring CC endothelial and smooth muscle cells by inhibiting apoptosis and promoting recovery of erectile function [64]. ADSC–derived exosomes display in vitro proangiogenic properties, and restored erectile function in vivo, by the proliferation of endothelial cells and decreasing fibrosis of CC.

Molecular mechanisms underlying MSC dysfunction

The accumulation of AGEs is one of the recognized mechanisms of MSC dysfunction in diabetes. In short, the formation of AGEs due to the overproduction of Reactive Oxygen Species (ROS)[29] mediates the intracellular glycation of mitochondrial respiratory chain proteins and triggers a cascade of events through activation of the receptor for RAGE [24,100,101]. Hyperglycemia exerts metabolic stress, leading to the production of AGE and the generation of ROS. In turn, mitochondrial DNA polymerase–γ mutations are stimulated, and ROS production is exacerbated. The apoptosis and senescence of stem/progenitor cells contribute to these pathological effects of diabetes. Chronic RAGE stimulation causes defects in cellular membrane repair [102]. This triggered damage via oxidative and endoplasmic reticulum stress by ROS production and increases inflammation through TNF–α signaling [100–102]. The effect of AGEs on BM–MSC function results from amplified oxidative stress and inflammatory response [23,103,104]. It is unclear whether the beneficial effects of in vitro preconditioning

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can be sustained when MSCs are transplanted into a hostile environment. Together, these studies suggest that the use of anti-inflammatory and antioxidant agents should be concurrently employed in patients with diabetes undergoing MSC therapy.

**Future perspectives**

The effects and safety issues for diabetes-associated ED treatment need further delineation to improve the quality of life for afflicted men.

Metabolic disorders are commonly observed after the pathological effects of diabetes have occurred [105]. The loss of penile smooth muscle and impaired vasculogenesis in patients with diabetic ED can hopefully be reversed by MSC regenerative therapy. However, issues to be considered include cellular senescence due to hyperglycemia–induced metabolic changes caused by epigenetic changes. In this condition, post-translational histone modification, DNA methylation, and regulation by noncoding RNA–like miRNA and IncRNA have reduced the regenerative abilities of MSCs. Similarly, exosomes regulate the efficacy of endogenous/transplanted cells and carry the molecular cargo that influences the angiogenesis of the diabetic penis. The regenerative ability of diabetic stem/progenitor cells is affected by reduced secretion of therapeutic exosomes or the aberrant release of diseased exosomes.

Progress to enable cell differentiation to include increasing the yield of cells, enabling grafting via direct cell or tissue transplantation and overcoming legal issues regarding national regulations [106].

In regenerative medicine, MSCs that can differentiate and migrate are a necessity. Paracrine action is vital to realize the curative effect of MSCs to improve erectile function. LESWT, in theory, recruits endogenous SC to the cavernous bodies to improve the diabetic microenvironment in the CC, and possibly the diabetic penis. The regenerative ability of diabetic stem/progenitor cells is affected by reduced secretion of therapeutic exosomes or the aberrant release of diseased exosomes. Progress to enable cell differentiation to include increasing the yield of cells, enabling grafting via direct cell or tissue transplantation and overcoming legal issues regarding national regulations [106].

A wide range of growth factors is secreted by ADSCs, and these, in turn, stimulate tissue regeneration. In clinical applications, the use of ADSCs is a reasonable concept for the repair of damaged tissues and the stimulation of angiogenic activity. Hypoxia preconditioning might also improve the therapeutic efficacy of ADSC in diabetes–induced ED. Additional issues to consider are unwanted side effects, the survival rate of ADSC in cavernous tissues, and changes that occur to ADSC in the cavernosal microenvironment [23].

Further discovery of the pathophysiological mechanisms will come. SPIONs effectively incorporated into ADSCs had no adverse effects on SC properties. ADSCs and platelet-rich plasma co–transplantation is another novel approach to cell therapy in regenerative medicine.

Platelet–rich plasma can enhance the properties of ADSCs and also needs further investigation [108]. Conversely, the processes related to culturing and isolating ADSCs have boundaries; these comprise the high cost of amenities and staff, the underlying threat of contamination with undefined proteins and foreign serum, and changes in functional characteristics due to repeated culturing procedures [109,110].

Soluble factors released from MSCs may benefit MSC effects [111]. High levels of cellular senescence, apoptosis, and altered differentiation capacity in ADSC isolated from type-2 diabetics, have been observed [112]. Thus, the addition of adjuncts that increase differentiation and proliferation is needed to fortify ADSCs.

Modification of MSCs with growth factor genes may enhance the efficiency of MSC therapy. Groups treated with modified MSCs demonstrated better erectile function than that is unmodified. Among these strategies, MSC-based treatment is the most promising due to its ability to recover function in cells and tissues.

The investigational procedures of ADSC and BM–MSC are similar when comparing studies with only minor alterations regarding the cells examined and monitored. ICP–measured, post–SC injection into the CC is significantly higher than the control populations. The addition of specific growth factors to SCs by gene transfection may recover the efficacy of damaged cells. Until now, no reproducible tracking markers of these cells have been developed. The encouraging effect by injection of SCs on the ICP is attributed to cellular transdifferentiation, and various paracrine effects [113]. The positive impact of the injection of SCs on the ICP belongs to the cellular transdifferentiation effect and particularly to the paracrine effects, which have not yet been understood [114].

The pathogenesis of diabetes mellitus may induce intrinsic MSC dysfunction that eventually will be unsuccessful. This highlights the need for a strategy to counteract the functional decline of MSCs. Compromised BM–MSCs may be ineffective, as impairment of BM–MSCs may lead to disease progression and the development of comorbidities. The emergence of autologous MSC therapy in diabetes necessitates a deeper understanding of the SC alterations that occur when these cells are chronically exposed to a pathological environment. Future studies need to mimic the changes in MSC in diabetes and either rectify them before transplantation or prevent them from occurring. There is still a need for preclinical studies investigating the efficacy of antioxidants and anti-inflammatory agents in reversing the functional decline of MSCs [23]. Chronic RAGE exposure induces changes in cellular membrane repair, triggers intracellular damage by causing oxidative and endoplasmic reticulum stress through elevations in cytosolic ROS production, and amplifies inflammation through NFκB–mediated TNF–α signaling. The RAGE signaling pathway may be a pivotal point to preserve SC function in diabetic ED.

As type–2 diabetes is a multifactorial disease that is associated with insulin resistance–induced hyperglycemia [23], the majority of preclinical MSC studies in diabetic ED have
focused on type-1 diabetes, which is an autoimmune condition characterized by a complete loss of insulin secretion, leading to hyperglycemia. Therefore, the development of autologous MSC therapies depends on a better understanding of the extrinsic host milieu on MSC function.

Advancements in technology and experimental techniques have provided an insight into how aging affects the properties of MSCs. Given that human life expectancy is expected to increase, the topic of cell aging and therapeutic applications continues to be an area of interest.

The more recent evidence suggests a developmental affiliation between pericytes and MSCs based on cell markers and differentiation potential[115, 116]. As a novel stem cell source, pericytes are generally considered to be the origin of MSCs. Pericytes have crucial roles in blood vessel function/stability, angiogenesis, endothelial cell proliferation/differentiation, wound healing, blood–brain barrier function, and hematopoietic stem cell maintenance [117]. All of these properties make pericytes preferred cells in the field of tissue engineering. Similar to other types of stem cells, pericytes act as a repair system in response to injury by maintaining the structural integrity of blood vessels[118]. Pericytes have recently been recognized for their central role in blood vessel formation. Pericytes are multipotent cells that are heterogeneous in their origin, function, morphology, and surface markers. In situ, pericytes are recognized by their localization to the abluminal side of the blood vessel wall and closely associated with endothelial cells, in combination with the expression of markers such as CD146, neural glial 2, platelet derived growth factor receptor β, α-smooth muscle actin, nestin and/or leptin receptor[116]. Similar to other types of stem cells, pericytes act as a repair system in response to injury by maintaining the structural integrity of blood vessels. The role of pericytes is not restricted to the formation and development of the vasculature: they have been shown to possess stem cell–like characteristics and may differentiate into cell types from different lineages. While this assumption relies mainly on indirect evidence, the data supports the possibility that a precursor of the MSC is natively associated with the blood vessel wall and belongs to a subset of perivascular cells. Addressing this aspect may help improve the novelty of the subject in diabetes.

**Conclusion**

Though few stem cell–based studies have been directed toward type-2 diabetes, MSC–based therapies may provide better multifaceted metabolic corrections and concurrently offer long–term benefits to diabetic patients (Figure 1). MSC therapy in diabetic men with ED appears very close to addressing the effectiveness and safety of regenerative technology (Figure 1) [119]. MSC seems to be safe and effective in the shorter term and may provide genomic or epigenetic changes in the longer term.

It is useful for future MSC clinical trials to include histology confirmation and more extensive multicenter trials with various study protocols to compare treatment templates, including dose, duration, and a number of MSC injections[120]. Adult MSC has the advantage of avoiding the ethical issues of ESCs, and besides, published literature shows a very low probability of malignant transformation and tumor formation [121]. Diabetic patients need to be counseled and treated for many problems [122] hopefully, and regenerative effects will soon be brought into clinical practice.

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