Nowadays, erectile dysfunction (ED) can only be managed with symptomatic treatments. Regenerative medicine, which is based on administering stem cells, has the potential to provide the first curative treatment for ED. Two types of stem cells were tested preclinically in animal models, namely mesenchymal (stromal) stem cells isolated from either bone marrow or adipose tissue. The application of both cell types yielded positive effects in various animal ED models. In acute animal models, such as cavernous nerve injury-induced ED, neither engraftment nor differentiation was observed, and stem cells are believed to interact with the host tissue in a paracrine fashion. In chronic disease models, some evidence suggested that engraftment and paracrine factors might boost function improvement. Clinical trials are currently enrolling patients so as to confirm the beneficial effects observed in rodents. If confirmed, this could pave the way for a broad use of stem cell therapy and thus revolutionize the treatment of ED.

**KEY WORDS**

Dysfunction erectile, therapy mesenchymateuses, cellules souches, médecine régénérative, vieillissement, diabète, lésion du nerf caverneux

**What is already known about the topic?**

Nowadays, erectile dysfunction (ED) can only be managed with symptomatic treatments. Using stem cells in the treatment of ED has been proposed, as it is likely to become a revolutionary new therapeutic option.

**What does this article bring up for us?**

The application of two stem cell types yielded positive effects on ED in various animal models. In acute animal models, such as cavernous nerve injury-induced ED, neither engraftment nor differentiation was observed, and stem cells are believed to interact with the host tissue in a paracrine fashion. In chronic disease models, some evidence suggested that engraftment and paracrine factors might boost function improvement. In this article, the preclinical and clinical results of stem cell application in ED are presented, and future perspectives are discussed.

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**Que savons-nous à ce propos ?**

Aujourd’hui, la Dysfonction Erectile (DE) ne peut être traitée que symptomatiquement. L’administration de cellules souches dans le traitement de la DE a été proposée et pourrait constituer une avancée thérapeutique révolutionnaire.

**Que nous apporte cet article ?**

L’utilisation de deux types de cellules souches a permis de démontrer des effets bénéfiques sur la fonction érectile de différents modèles animaux. Dans les modèles de lésion des nerfs caverneux, la prise de greffe et la différenciation n’ont pas été observées et les cellules souches sont supposées interagir avec la tissu de manière paracrine. Dans les modèles chroniques, des arguments suggèrent que l’engraftment et les facteurs paracrines peuvent booster la fonction. Cet article fournit une revue des résultats précliniques et cliniques de l’utilisation des cellules souches dans le traitement de la DE et élabore une discussion sur les perspectives futures.
INTRODUCTION

Erectile dysfunction is defined as the inability to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse (1). Erectile dysfunction affects men from 40 years of age with age-associated increase in prevalence up to 50–100% in men older than 70 years (2). There are a large number of disorders known to contribute to the development of erectile dysfunction including but not limited to diabetes, hypogonadism, metabolic syndrome, cardiovascular disease, pelvic nerve injury, and other local disorders, such as Peyronie’s disease. Understanding of molecular pathogenesis has successfully resulted in widespread use of phosphodiesterase type 5 (PDE5) inhibitors. As these drugs interfere with the nitric oxide–cyclic guanosine monophosphate pathway, an intact nitric oxide supply from the nerves and endothelium is needed to guarantee the efficacy of these agents. Several prevalent diseases reduce the bioavailability of nitric oxide, including severe diabetes and denervation of erectile tissue due to radical prostatectomy, which results in degeneration of nitrinergic nerves supplying the penile corpora cavernosa and vasculature. Men with these underlying disorders commonly do not respond well to PDE5 inhibitors. The current available treatment modalities are providing solely symptom relief and do not cure the underlying disease. A cure for erectile dysfunction resulting in spontaneous unassisted intercourse entices research into novel regenerative treatment methods, including stem cells. (3)

STEM CELLS

Stem cells are undifferentiated cells that are capable of self-renewal and differentiation along different specialized cell types. Based on these two essential properties, stem cells have been used as a therapeutic agent based on the assumption and observation that exogenously administered stem cells are able to engraft in the diseased host tissue, where they further divide and differentiate to give rise to a healthy new cell population to replace those populations destroyed by disease or injury (‘building block theory’). However, recent research illustrates that certain widely used stem cell populations, such as mesenchymal multipotent cells, may exert their beneficial effects through a paracrine-dependent fashion rather than by engraftment and differentiation (‘paracrine theory’) (4) Stem cells secrete large amounts of factors, which have angiogenetic, trophic, inflammatory modulating, and antifibrotic and chemotactic properties. It has even been shown that stem cells are able to secrete RNA in microvesicles as a method of influencing their host environment. (5)

Stem cells are classified by their developmental capacity as totipotent, pluripotent, multipotent, progenitor, and precursor cells. Totipotent cells in zygote and morula develop into completely differentiated organisms, and in extraembryonic tissues such as the placenta. Pluripotent cells divide into all three germinal layers (ectoderm, mesoderm, and endoderm) but do not produce extraembryonic tissue (6). The classical and most well known examples of pluripotent cells are embryonic stem cells (ESC). The use of ESCs in research has been limited as a result of ethical concerns as it requires destruction of embryos. Multipotent stem cells include hematopoietic and mesenchymal/stromal stem cells, which can essentially differentiate into any daughter cell within their own germinal layer. Unipotent cells are progenitor or precursor cells with limited proliferation potential and are able to differentiate into one or several specific cell types (7).

Stem cell types reported in erectile dysfunction research mainly include adipose tissue-derived stem cells (ADSCs), bone marrow-derived stem cells (BMSCs), and muscle-derived stem cells (MDSCs), although there are rare reports on the use of ESCs. Theoretically, these cells can differentiate into all cell types of the mesodermal origin, including muscle, fat, and bones, although extralinear differentiation has been shown in vitro (8).

Bone marrow aspiration yield BMSCs for injection either after culture or uncultured as whole mononuclear fraction, of which 83 per million cells are mesenchymal stem cells (MSCs) (9). ADSCs from adipose tissue are easily harvested, either as a component of the so-called ‘stromal vascular fraction’ (SVF) (stem cells in adipose tissue reside in the perivascular niche, containing around 560 MSCs per million cells, or as a purified stem cell population after successive culturing (9). Adipose tissue is easily harvested in large amounts without major adverse events, and this can be done under local anaesthesia by liposuction. Harvested fat tissue or liposapirate is processed mechanically and incubated with collagenase to remove the extracellular matrix. Mature adipocytes are separated by centrifugation, and pelleted SVF cells isolated, which can then be reinjected in the patient or used for isolation and expansion of ADSCs. Automated closed-top devices for the isolation of SVF have been developed and are already used in the clinical setting for different indications (10).

ACUTE ERECTILE DYSFUNCTION: CAVERNOUS NERVE INJURY

Iatrogenic trauma of the neurovascular bundle as a result of radical prostatectomy is a frequent cause of erectile dysfunction. This complication remains frequent despite a refinement of nerve-sparing operative techniques including the introduction of robot-assisted laparoscopy (11). Cavernous nerve injury (CNI) may result in neuroapraxia due to compression, temporary ischemia, or axonotmesis due to stretching, crushing, or contusion. In cases of neuroapraxia, no Wallerian degeneration occurs and a recovery of nerve function can be expected within weeks or months. In case of axonotmesis, Wallerian degeneration causes progressive disintegration and breakdown of the axons despite an intact nerve sheet (11).
This causes temporal denervation resulting in apoptosis of endothelial and smooth muscle cells in the corpus cavernosum. Smooth muscle is replaced by collagen and fibrosis, leading to veno-occlusive dysfunction and eventually resulting in erectile dysfunction (11). A more severe neural insult is neurotmesis, in which continuity of the entire nerve is lost. This mechanism typically occurs in cases of nerve transaction and is associated with the worst prognosis for recovery (11).

Bochinski et al. first published in 2004 injection of green fluorescent protein-labeled ESC either into the corpus cavernosum or adjacent to the major pelvic ganglion (MPG) in rats with cavernous nerve injury (12). Erectile function improved significantly. Neurofilament and neuronal nitric oxide synthase staining showed increased neuroregeneration or nerve preservation compared to controls. No significant incorporation of cells neither in the erectile tissue nor in the MPG was evident.

The results found by Bochinski with ESCs were confirmed by both Kendirci et al., administering BMSC with or without selecting for expression of the P75 nerve growth factor receptor (13), and Albersen, administering ADSCs from the perivascular compartment of the rats own abdominal adipose tissue (14), resulting in EF improvement in both studies. Interestingly, in both studies no engraftment or differentiation in the host tissue was seen. An improvement in EF was also observed after injection of ADSC lysate (14) and MSC were found to secrete neurotrophic factors. Furthermore, an in-vitro study showed that ADSC-conditioned medium increases neurite outgrowth in MPG culture (15). The findings of these studies indicate that stem cells exert their beneficial effects on the host tissue in a paracrine fashion and mark a paradigm shift, as the mechanism of action of stem cells was previously believed to be engraftment, differentiation and repopulation of the diseased organ.

Further investigation has elucidated how mesenchymal stem cells improve EF recovery after nerve injury. After intracavernous administration, ADSCs quickly disappear from the corpus cavernosum and preferentially migrate to the bone marrow (16). However, when an injury is present, such as crush of the CN, ADSC migrate to the site of injury, the MPG (17). There, at the site of injury, they act as a local factory of molecules, promoting neuroregeneration, modulating the inflammatory response and reducing of scar formation.

LONG-TERM ERECTILE DYSFUNCTION MODELS: DIABETES, AGING, AND METABOLIC SYNDROME

Therapeutic application of stem cell has been investigated in chronic disease models of erectile dysfunction including aging, diabetes mellitus, and hyperlipidemia. In chronic erectile dysfunction the mechanism of action is presumed to be by engraftment and transdifferentiation, differing from the paracrine action seen in acute disease models such as CNI.

Bivalacqua et al. first reported that endothelial nitric oxide synthase (eNOS)-modified BMSCs injected in aged rats of 25 months improved erectile function (18). This improvement occurred with injection of both unmodified and modified MSCs, but occurred faster with eNOS-modified BMSC injection. Endothelial dysfunction with decreased levels of vasorelaxant nitric oxide is believed to be a major contributor to erectile dysfunction in aging. In this study, improved erectile function was associated with increased eNOS protein levels, NOS activity, and cGMP levels in the corpus cavernosum, pointing at improvement of endothelial integrity. Abdel Aziz and coworkers reported that the effect of intracavernous BMSC on erectile function was seen for up to 3 – 4 months and showed persistence of stem cell in the erectile tissue. As no colocalization of these cells with endothelial or smooth muscle cell-specific markers was performed, no definite proof for transdifferentiation and incorporation could be given (19).

Diabetes mellitus resembles the pathophysiology of erectile dysfunction seen in aging in many aspects with the same essential components needed for erection being affected: vascular endothelium, nitrergic innervation, smooth muscle and cavernosal compliance. Autologous ADSCs administration in type 2 diabetes rats showed significantly better erectile responses to CNS at 21 days after injection. Only a small number of EdU-labeled cells were detected within the corpus cavernosum tissue and no engraftment of these cells in the host tissue was seen (20). Injection of BMSCs in type 1 diabetic animals induced by streptozotocin resulted in increased intracavernous pressure (ICP) response on CNS and improved expression of neuronal markers (21). A follow-up study from the same group was able to obtain a similar improvement in neuronal markers when injecting BMSC-conditioned medium instead of BMSCs, suggesting a paracrine effect. Application of stem cells in a disease model of metabolic syndrome, the most common seen form of erectile dysfunction, resulted in improved erectile function recovery paired with increased endothelial and neural function. Remarkably, no significant engraftment of stem cells that would explain transdifferentiation and replacement of the diseased tissue as the therapeutic mechanism of action behind the improved erectile function was seen (22).

In contrast to acute models of erectile dysfunction such as CNI, chronic erectile dysfunction models do not have a single temporally defined acute injury occurring with release of chemokine factors and initiating a cascade of signalling pathways. Contributing to this is the fact that these chronic conditions affect the erectile function at several levels and cell types whereas in acute injury there is one defined inciting event that can be targeted at the moment of injury. Following, the mechanism of action of stem cell therapy is much harder to investigate in chronic disease models. Some studies have suggested engraftment and transdifferentiation of stem cells to be responsible for erectile function improvement whereas others suggested a paracrine effect.
Both BMSCs and ADSCs have ample preclinical data; nevertheless, several crucial issues must be addressed prior to therapeutic application of stem cells. First, which type of stem cell would be the most appropriate considering factors such as cost, ethical issues, ease of isolation and culturing, risks, effectiveness, and source. Second, migration and survival of cells in the host tissue after administration as well as mode of action still needs important answers. Third, surveillance is needed for possible adverse effects of stem cell transplantation, as the potential effect on cell growth can affect a concomitant subclinical disorder (i.e., cancer).

Human data on stem cell therapy is emerging some 10 years after the first reports on animal models. Bahk et al. implanted of the adipose tissue umbilical cord stem cells in penis of seven men with diabetes-related erectile dysfunction. This study reported increased rigidity insufficient for penetration without addition of PDE5 inhibitors. (23) Various cellular products including MSCs, SVF, and BMSCs are currently being studied in clinical trials (NCT02087397, NCT02240823, NCT02414308, NCT02344849, NCT01089387, NCT02398370, NCT01953523, NCT02472431, NCT01983709, NCT01601353). You et al. reported a phase 1/2 trial of intracavernous bone marrow mononuclear cells in after radical prostatectomy erectile dysfunction. (24) This study enrolled 12 participants with penile arterial insufficiency and/or veno-occlusive dysfunction at 6 months to 3 years after treatment for localized prostate cancer. As the design of this trial was mainly phase I, the safety outcome is the main conclusion that can be drawn from the study and no serious adverse events were noted. There were no significant adverse reactions and no signs of cancer recurrence. An increase in Doppler peak systolic velocity was seen, but as no control group or placebo was used, it is unclear if this recovery is due to the therapeutic effect of stem cells or the natural recovery occurring after surgery. Larger phase II and III trials in the future will need to answer this question. (25)

**CONCLUSION**

Stem cells have beneficial effects on restoration of erectile function through paracrine effects and cellular mechanisms. Application of stem cells for treatment of erectile dysfunction is entering an exciting new dawn with preliminary clinical trials. Basic research and clinical trials in various disease states are required to define the role of stem cells therapy in the treatment line-up.


LES EFFETS INDÉSIRABLES...
CHEZ LES PATIENTS ATTEINTS DE MALADIE CORONARE

DIMINUATION DU RISQUE D’ÉVÉNEMENTS CV


1. DENOMINATION DU MEDICAMENT ATOZET 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg comprimés pelliculés. 2. COMPOSITION QUALITATIVE ET QUANTITATIVE Chaque comprimé pelliculé contient 10 mg d’atorvastatine calcique trihydraté et 10 mg d’ézetimibe. 3. PHARMACIENNE Comprimé pelliculé. 4.2 POSOLOGIE et mode d’administration Posologie Hypercholestérolémie familiale homozygote ATOZET est indiqué comme traitement adjuvant au régime chez les patients adultes ayant une hypercholestérolémie primaire (familiale hétérozygote et non familiale) ou une dyslipidémie mixte lorsque l’utilisation d’une ou plusieurs autres thérapeutiques non répétées de façon appropriée par une stratégie d’ajustement, patients souffrant déjà d’une rate et d’atromboplasie. Hypercholestérolémie familiale homogyzote (HFPa) ATOZET est indiqué comme traitement adjuvant chez les patients adultes ayant une HFPa. Ces patients peuvent recevoir également des traitements adjuvants (par ex. aphérèse des LDL). 4.4 POSOLOGIE et mode d’administration Posologie Hypercholestérolémie familiale homogyzote ATOZET est indiqué comme traitement adjuvant au régime chez les patients adultes ayant une HFPa. Ces patients peuvent recevoir également des traitements adjuvants (par ex. aphérèse des LDL). 4.4 POSOLOGIE et mode d’administration Posologie Hypercholestérolémie familiale homogyzote ATOZET est indiqué comme traitement adjuvant au régime chez les patients adultes ayant une HFPa. Ces patients peuvent recevoir également des traitements adjuvants (par ex. aphérèse des LDL). 4.4 POSOLOGIE et mode d’administration...