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REVIEW

Stem-cell therapy for erectile dysfunction

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KEYWORDS

Ageing;
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Diabetes;
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ABBREVIATIONS

ED, erectile dysfunction;
PD, Peyronie's disease;
CNI, cavernous nerve injury;
RP, radical prostatectomy;
CC, corpus cavernosum;
PDE5 (I), phosphodiesterase type 5 (inhibitor);

Abstract ***Introduction:*** Erectile dysfunction (ED) is the most common sexual disorder that men report to healthcare providers, and is the male sexual dysfunction that has been most investigated. Current treatments for ED focus on relieving the symptoms of ED and therefore tend to provide a temporary solution rather than a cure or reversing the cause. Recently, therapies based on stem cells (SCs) have had an increasing attention for their potential to restore erectile function. Preclinical studies showed that these cells might reverse the pathophysiological changes leading to ED, rather than treating the symptoms of ED. This review is intended to provide an overview of contemporary reports on the use of SCs to treat ED.

Methods: We made an extensive search for reports on SC-based therapy for the management of ED, published in English between 1966 and 2013, using the search engines SciVerse-sciencedirect, SciVerse-scopus, Google Scholar and Pubmed, with the search terms 'erectile dysfunction', 'stem cells', 'multipotent stromal cells', 'adipose (tissue) derived stem cells', 'bone-marrow derived stem cells', 'animal model', 'diabetes', 'ageing', 'Peyronie's Disease' and 'cavernous nerve injury'.

Results: Fifty-four papers were identified and contributed, either as an original research report or review thereof, to this review. Several preclinical studies addressed SC-based therapies for the recovery of erectile function caused by a variety of both chronic and acute conditions. Overall, these studies showed beneficial effects of SC therapy, while evidence on the mechanisms of action of SC therapy varied between

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NO, nitric oxide;
(e)(n)NOS, (endothelial) (neuronal) NO synthase;
(A)(E)(H)(M) SC, (adult) (embryonic) (haematopoietic) (mesenchymal) stem cell;
AD, adipose tissue-derived;
BM, bone marrow-derived;
MD, muscle-derived;
SVF, stromal vascular fraction;
MPG, major pelvic ganglion;
GFP, green fluorescent protein

studies. One clinical trial investigated the short-term effects of SC therapy in diabetic patients with ED. Two more clinical trials are currently recruiting patients.

Conclusions: The rapidly expanding and highly promising body of preclinical work on SC-based medicine providing a potential cure for ED, rather than merely symptom relief, is indicative of the increasing interest in regenerative options for sexual medicine over the past decade. Clinical trials are currently recruiting patients to test the preclinical results in men with ED.

Introduction

Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual intercourse [1]. Notwithstanding variations in definitions and methods, various large-scale studies (both cross-sectional and longitudinal) confirm the global presence of this disease, with an estimated overall prevalence rate of 10–20% worldwide [2]. There is a strong correlation between age and ED, with the prevalence increasing steadily from 6.5% in men aged 20–39 years to 77.5% in those aged $\geqslant$75 years. While previously ED was believed to be primarily due to psychological causes, currently the vast majority of cases have been attributed to the underlying organic disease [3]. In many cases ED is the result of systemic changes in diseases such as diabetes and atherosclerosis, and in the (patho)physiological process of ageing, as illustrated by the convincing epidemiological data cited above [4]. However, also more localised diseases have been linked to ED, such as Peyronie's disease (PD), and iatrogenic causes such as cavernous nerve injury (CNI) during radical prostatectomy (RP) for clinically localised prostate cancer [5]. RP results in significant damage to the neurovascular bundles and autonomic innervation of the penis, resulting in 'either-or-not' temporary denervation of the penis and severe end-organ damage, as evidenced by smooth muscle apoptosis and fibrosis of the corpus cavernosum (CC) [6]. The latter type of ED has been extensively investigated in the light of the possible application of stem cell (SC) therapy for the cure of ED [7].

The recognition of nitric oxide (NO) as the main erectogenic (gaso)transmitter in the erectile tissue has led to the development of phosphodiesterase type 5 (PDE5) inhibitors (PDE5-i) [8]. The efficacy of PDE5-i depends on the integrity of the NO pathway, so it is clear that patients in whom this pathway is deranged or defective might benefit much less than would the general population from treatment with PDE5-i [2]. Diseases in which the availability of NO is reduced include severe diabetes with neuropathy and endothelial dysfunction, metabolic syndrome, and down-regulation or deactivation of NO synthase (NOS) expression, which can occur in denervation of the erectile tissue after RP, atherosclerosis, advanced age, and hypogonadism [2]. Furthermore, in severe ED there is also a downregulation of targets activated by the NO pathway [9]. Overall efficacy rates of PDE5-i are currently 60–70% with on-demand treatment regimens [10]. Men who persistently fail to respond to PDE5-i might require intracavernous injections of vasoactive substances, e.g. prostaglandin E1 and papaverine, to regain erectile function, and when these treatments fail patients must resort to the surgical implantation of inflatable penile prostheses. It is clear that current pharmacotherapies for ED are aimed at providing symptom relief and do not represent a curative approach [11]. Despite this, patients report that the most important treatment outcome and measure of success is the ability of a therapy for ED to cure them of their disease [12]. Thus an ideal future therapy for ED would focus on identifying a disease-specific therapy with curative intent. Various groups worldwide are currently involved in investigating how cell-based therapy, specifically SCs, might be of use in reversing different pathophysiological processes in the establishment of ED to halt or reverse the development of this prevalent sexual dysfunction. While these studies are mainly conducted in a preclinical setting, clinical trials are starting to emerge based on positive preclinical results, and the outcome of these studies might change the approach towards ED.