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Stem cell treatment of erectile dysfunction ☆,☆☆

Amjad Alwaal [a,b,*], Uwais B. Zaid [a], Ching-Shwun Lin [a], Tom F. Lue [a]

[a] Department of Urology, University of California, San Francisco, CA, USA
[b] King Abdul Aziz University, Jeddah, Saudi Arabia

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ABSTRACT

Erectile Dysfunction (ED) is a common disease that typically affects older men. While oral type-5 phosphodieserase inhibitors (PDE5Is) represent a successful first-line therapy, many patients do not respond to this treatment leading researchers to look for alternative treatment modalities. Stem cell (SC) therapy is a promising new frontier for the treatment of those patients and many studies demonstrated its therapeutic effects. In this article, using a Medline database search of all relevant articles, we present a summary of the scientific principles behind SCs and their use for treatment of ED. We discuss specifically the different types of SCs used in ED, the methods of delivery tested, and the methods attempted to enhance SC therapy effect. In addition, we review the current preclinical literature on SC therapy for ED and present a summary of its findings in addition to the single clinical trial published.

Contents

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* Corresponding author at: University of California, San Francisco, Box 0738, 1600 Divisadero St., MZ Bldg A, Room A609, San Francisco, CA 94143, USA. Tel.: +1 415 885 7748; fax: +1 415 885 7443.
E-mail address: amjadwal@yahoo.com (A. Alwaal).

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1. Introduction

1.1. ED

It is an important health problem that significantly impacts the patient's quality of life and can have a detrimental effect on his well-being and relationship with his partner [1]. ED is defined as the inability to achieve or maintain a penile erection satisfactory for sexual intercourse [2]. ED is estimated to affect 20% of men above 40 years of age, with the incidence increasing with increasing age [3], in addition to other factors such as better diagnosis and increased awareness of the disease [4]. Men between the age of 61–70 years are twice as likely to be affected than men aging 51–60 years [5], with 67% of men at age 70 years affected with the disease [6]. Another important reason for the rise in ED is the rapidly growing prevalence of diabetes mellitus (DM) [7], which is a major risk factor for ED [4]. Several treatment modalities exist for ED, including oral PDE5Is, intraurethral alprostadil suppository, intracorporal (IC) injection of erectogenic medications, vacuum device, and penile implant. Among these modalities, PDE5Is remain the most widely used and have great success rates, mainly due to their ease of administration as oral medications and proven efficacy. However, despite such successes, there are several limitations to their use. For example, they are contraindicated in some patients who take nitrates due to the risk of developing severe hypotension; some men cannot tolerate their side effects; they are only partially effective in certain patients; and they have a considerable financial cost [8]. In addition, they provide only symptomatic relief of ED and do not offer a cure for the disease. Therefore, there is a growing interest in developing therapies that offer a cure for the disease, including gene therapy and SC therapy [9,10].

1.2. Mechanism of erection

Penile erection occurs through a nitric oxide (NO)-mediated mechanism. NO, the main neurotransmitter involved in erection, is released by endothelial cells and non-adrenergic non-cholinergic nerve terminals in the cavernosal tissue. It causes relaxation of the cavernosal smooth muscles through a cGMP-mediated reduction of intracellular calcium, after which cGMP gets degraded by PDE5 [11]. Once the lacunar spaces are filled with blood, they compress the subtunical venules, resulting in erection. Detumescence occurs when adrenergic receptors are activated, inducing contraction of the cavernosal smooth muscles with resultant diminished blood in-flow and reduced size of the lacunar spaces, which in turn allows more venous out-flow through the subtunical venules [12].

1.3. Aging and ED

Different diseases and conditions cause ED through different mechanisms. Aging results in ED through increased penile vascular tone [13] and inactivation of endothelial nitric oxide synthase (eNOS), the latter of which is accomplished by decreased phosphorylation of eNOS positive regulatory site and increased phosphorylation of its negative regulatory site [14]. In addition, it reduces nNOS nerve fibers, thereby diminishing the erectile response to cavernosal nerve stimulation and reducing penile reflexes [15]. Aging also decreases NO bioavailability by increasing reactive oxygen species (ROS). When ROS are in excess, superoxide anion interacts with NO to cause endothelial dysfunction [16,17]. Aging was also found to be associated with abundance of collagen fibers, reduction of smooth muscle cells, and degenerative changes in elastic fibers [18].

1.4. Metabolic syndrome

The prevalence of DM in the US is 8.3% of the population, with 26.9% of the population 65 years or older affected with DM in 2010 [19]. Diabetics are 3 times more likely than non-diabetics to have ED [5], with a prevalence of 50–75% [6]. ED affects diabetics 10–15 years earlier than non-diabetics [5], and PDE5Is are less efficacious in this population [20]. The mechanism by which DM causes ED is multifactorial and there are different findings and proposed mechanisms for its occurrence. DM was found to diminish the amount of NO-releasing penile nerves [21,22], cavernosal endothelial cells, and cavernosal smooth muscle content [22,23]. Ning et al. [24,25] recently demonstrated that hyperglycemia induced mitochondrial fragmentation and cellular apoptosis of endothelial cells. Hyperglycemia is also associated with smooth muscle dysfunction through oxidation of low-density lipoproteins and excessive production of oxygen free radicals. DM also impairs vascular endothelial growth factor (VEGF) signaling and upregulates the RhoA/RhoKinase pathway [26–28]. It also reduces the expression and activity of neuronal nitric oxide synthase (nNOS) [29–31]. Given the penile tissue damage associated with DM and the negative impact of ED on the quality of life in diabetics [32], SC therapy holds a great promise to treat DM-associated ED due to SCs' regenerative ability and their potential to restore cavernosal endothelial and smooth muscle cells. Hyperlipidemia is another metabolic factor responsible for ED [33]. It was found that for every 1 mmol/L increase in serum total cholesterol there was a 32% increased risk of ED, and for every 1 mmol/L increase in high-density lipoprotein (HDL) there was a marked reduction in the risk of ED [34]. Hyperlipidemia causes ED through neuronal and endothelial dysfunction, leading to a reduction in cavernosal NO levels [35–37].

1.5. Prostate cancer therapy-related ED

Prostate cancer is the most commonly diagnosed cancer in US men [38]. Earlier detection and treatment have allowed the widespread use of localized treatment options in about 80% prostate cancer patients [38], including radical prostatectomy (RP) and radiation therapy (RT) [39]. However, these treatment options carry a significant risk of post-treatment ED [40]; for example, RP is associated with 60.8–93.9% risk of ED [41]. The most widely accepted mechanism for post-RP ED is injury to the cavernosal nerve fibers that run along the posterolateral aspect of the prostate. Nerve-sparing RP has been introduced in order to preserve the cavernosal nerves. However, despite the continued refinement in the surgical technique, nerve-sparing RP is still associated with nearly 20% risk of ED at 24 months post-op [42]. This is likely due to neurapraxia, in which stretching, heating, or trauma to the cavernosal nerve fibers during surgery induce Wallerian degeneration [43]. Alternatively, NO-releasing nerves stop producing NO during the period of neurapraxia, resulting in cavernosal smooth muscle apoptosis and fibrosis. In support of this theory is the reduction of smooth muscle content and subsequent fibrosis in post-RP penile tissue [43,44]. RT has been much less studied than RP, but generally from the limited data published, it is likely that post-RT ED follows the same mechanism. That is, cavernosal nerve injury followed by smooth muscle degeneration [23,45]. PDE5Is are being prescribed routinely in many centers post-RP as part of the "penile rehabilitation protocol". The exact mechanism for their effect is not known, as PDE5 sits downstream of NO, which cannot be produced by damaged nerves post-RP. Thus, the exact mechanism for PDE5Is' effects in post-RP ED patients remains to be proven, and so does their true effect in this population [44,46].

1.6. Peyronie's disease (PD)

PD affects 3% of men, resulting in pain and penile deformities such as curvature, indentation, and shortening [47]. Although further research is needed, it is thought that PD causes ED directly. Among several mechanisms that have been proposed to describe this effect [48], veno-occlusive dysfunction resulting from the PD plaque is the most commonly accepted although further research is needed to prove this theory [49]. The severity of PD occasionally necessitates incising or excising the plaque followed by patch grafting the tunica albuginea (TA)