SEXUAL MEDICINE REVIEWS

Stem Cells in Male Sexual Dysfunction: Are We Getting Somewhere?

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ABSTRACT

Introduction: Stem cells for sexual disorders are steadily being introduced into clinical trials. Two conditions of importance are the main target for this line of treatment, especially when regarding the wide array of translational and basic science highlighting the potential advantages of regenerative therapy: erectile dysfunction (ED) and more recently Peyronie disease (PD). Cellular therapy offers a treatment modality that might reverse disease progression. It would be used in a curative setting, in contrast to other pharmaceutical agents that are currently available.

Aim: To review basic preclinical studies and recent clinical trials of stem cells on ED and PD.

Methods: A search of the medical literature for the following terms was performed using PubMed: *stem cells, cellular therapy, erectile dysfunction, Peyronie's disease,* and *clinical trial.*

Main Outcome Measures: A non-systematic narrative review and critical reflection on preclinical and clinical studies administering stem cells for ED and PD in animal models and human subjects.

Results: Numerous studies have confirmed the beneficial functional effects of stem cell injection in established animal models on ED and PD. Various stem cell types have been adopted, from embryonic to adult mesenchymal cell types. Each cell type offers distinctive advantages and disadvantages. Diverse administrations of stem cells were investigated, with insignificant variability in the ultimate results. Stem cells appear to have a pronounced paracrine effect, rather than the classic engraftment and differentiation hypothesis. Phase 1 clinical trials using stem cells have not reported any severe adverse events in animals. However, these results cannot be extrapolated to draw any conclusions about efficacy in human patients.

Conclusion: Stem cells have an established efficacy in preclinical studies and early clinical trials. Studies are currently being published demonstrating the safety of intrapenile injection of autologous bone marrow- and adipose tissue-derived stem cells.

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Key Words: Stem Cells; Progenitor Cells; Cavernous Nerve Injury; Peyronie Disease; Sexual Dysfunction; Erectile Dysfunction

INTRODUCTION

Erectile dysfunction (ED), defined as the inability to attain and maintain a penile erection sufficient for satisfactory sexual intercourse, is the most common male condition studied in sexual medicine.[1] There is an increasing prevalence of ED worldwide.[2,3] This trend is driven by an upsurge of underlying risk factors such as cardiovascular disease and generalized atherosclerosis, metabolic syndrome, diabetes mellitus, and increasing age. These factors contribute to microvascular and endothelial dysfunction.[4,5] In addition, ED after radical prostatectomy for prostate cancer is the most common iatrogenic cause of ED.[6,7] ED also can be a result of local disease or anatomic disturbance. Peyronie disease (PD) is a connective tissue disorder of the tunica albuginea. Unfortunately, the pathophysiology has not been completely elucidated. It is characterized by an initial inflammatory component and a secondary fibrotic deposition at the tunica albuginea. It can cause significant curvature, thus affecting the corpora cavernosa and leading to impaired sexual function. PD is often associated with ED because of the combined physical and psychological burden for the patient. Epidemiologic data have reported a large variety in prevalence, up to 20% in the diabetic population and up to 40% in the post-prostatectomy population.[8,9]

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Contemporary treatment of ED involves temporary stimulation of engorgement of the corpora cavernosa, rendering the treatment of ED a symptomatic and temporary one.[10] However, patients rate "curing" as the most important measurement of treatment success.[11] In addition, phosphodiesterase type 5 inhibitors rely on the bioavailability of endogenous nitrous oxide (NO) to exert their effects. However, patients with decreased NO bioavailability (eg, from nerve damage after radical prostatectomy or neurovascular damage in diabetes) respond poorly to this therapy. This accounts for current dropout rates of at least 50%.[12] These patients have to resort to more invasive treatment options such as intracavernous prostaglandin injections or implantation of penile prosthetic erection devices. Extracorporeal low-intensity shockwave therapy is a novel treatment option that seems to improve erectile function (assessed by the International Index of Erectile Function) in patients with mild ED. Nonetheless, according to a recent systematic review and meta-analysis, these effects appear rather limited and seem to decrease over time.[13] The introduction and increasing popularity of this treatment, even without supporting evidence, illustrates that patients are searching for more permanent ways to improve their condition and decrease the need for on-demand pharmacotherapy.

Among the various treatments viewed as regenerative medicine, stem cells (SCs) could be one of the up-and-coming curative treatment options for ED. Bochinski et al[14] first reported on the injection of embryonal SCs into rats with cavernous nerve injury (CNI) in 2004. Various groups since then have reported on the use of cells from non-embryonal tissue in acute and chronic animal models of ED.[15,16] This review is written in parallel with the second phase of SC research in sexual medicine with the advent of clinical trials.[17,18] Although the currently published data are limited to phase 1 clinical trials, thus allowing conclusions to be made only for safety in humans, cellular therapy is already being commercially offered for applications in sexual medicine.[19] Although the clinical application of cellular therapy is an exciting opportunity to find a cure for ED, researchers and clinicians should proceed with the necessary care and adhere to guidelines for testing, approval, and implementation before mainstream application and distribution. In this review, the available literature on preclinical and clinical application of SCs is thoroughly assessed. An attempt is made to provide guidance for further translation of this new line of therapy to daily practice.

STEM CELLS

SCs are defined by their self-renewal capability and differentiation potential. When an SC divides, the resulting daughter cells are an exact copy of the parent cell to maintain the SC population or differentiate into a more specialized cell type. A daughter cell that retains its means of self-renewal remains undifferentiated after repeated divisions. Various patterns of cell division can be recognized. When dividing "asymmetrically," a parent cell produces an exact copy of itself and another differentiated daughter cell. "Stochastic differentiation" means one parent cell divides into two differentiated cells and a second parent cell divides into two exact copies to maintain the SC population.

These alternative outcomes of cell division are the key principles in the maintenance of the SC population and the potential for tissue regeneration.[20]

A hierarchy exists in SC classification; they are known as totipotent, pluripotent, multipotent, progenitor, or precursor cells.[20] Cells in the zygote and morula stages have totipotent characteristics, meaning they can develop into a completely differentiated organism and extraembryonic tissue.

Embryonal SCs are a typical example of pluripotent SCs; they have the capability to produce cells from all germinal layers (ectoderm, mesoderm, and/or endoderm). Multipotent SCs can be readily isolated from fully grown organs, renew themselves, and differentiate into any cell type within their own germinal layer. Consensus definitions of SCs have been proposed with the growing interest in therapeutic applications.[21] In general, stromal cells are connective tissue cells descending from any organ system. An SC is defined by its ability for self-renewal and multipotent characteristics. In contrast, a progenitor cell has limited proliferation potential and can differentiate into at least one specific cell type.

Initial interest in SCs was driven by the potential therapeutic effect of these newly introduced cells replacing damaged or defective host cells. Nonetheless, evidence for engraftment and differentiation of cells has not been found. Improvement in erectile function has been observed with injection of SCs and cell lysate from harvested SCs, supporting a paracrine mechanism of action.[22] Mesenchymal SCs (MSCs) in particular secrete large amounts of angiogenetic, trophic, inflammation-modulating, antifibrotic, and chemotactic factors.[23] Immunoactivity of MSCs is mediated by secreted molecules and by direct cellular contact, which can influence the action of various cells, such as dendritic cells, B cells, and various T cells including T-regulatory cells, killer cells, and various T-helper cells.[24] Multiple molecular agents secreted by MSCs mediate immunomodulatory and trophic effects.[25] CXCL5, a cytokine produced by adipose-derived SCs (ADSCs), has been shown to exert neurotrophic effects on major pelvic ganglion (MPG) neurite outgrowth, potentially playing a role in CN regeneration.[26] Another hypothesis suggests there is active secretion of vesicles containing various forms of RNA. This could explain the paracrine influence of cellular processes in the direct environment of the SC.[27]

Cell types used in early SC research originated from embryos, which faced limited availability and ethical concerns. MSCs were subsequently isolated from various tissues, most commonly from bone marrow and adipose tissue.[28] These cells can differentiate into all cell types of mesodermal origin, including muscle, fat, and bone. Researchers also have explored SCs from other sources, including testicles and urine.[29,30] Stromal vascular