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Review Article

# Stem Cell Therapies for Neurogenic Erectile Dysfunction

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**Abstract**

Erectile Dysfunction (ED) is a condition associated with aging, diabetes, hypercholesterolemia, and neurological diseases. Neurogenic ED results from damage to nerves associated with erectile function. Stem cells can play a therapeutic role by regenerating tissues and restoring normal function in various diseases accompanied by neurogenic ED. Recently, stem cell technology has been used to study smooth muscle and endothelial cell repair in ED. In thisreview, we have focused on the potential application of stem-cell–based the rapiesin neurogenic ED.

**Keywords:** Neurogenic erectile dysfunction; Stem cell; Cell based therapy; Differentiation

## Abbreviations

ED: Erectile Dysfunction; ROS: Reactive Oxygen Species; ESCs: Embryonic Stem Cells; NESs: Neural Embryonic Stem Cells; MSCs: Mesenchymal Stem Cells; BM-MSCs: Bone Marrow-derived Mesenchymal Stem Cells; MDSCs: Muscle-Derived mesenchymal Stem Cells; ASCs: Adipose-derived Stem Cells; ICP, Intracavernous Pressure; STZ: Streptozotocin; VEGF: Vascular Endothelial Growth Factor; NCSCs: Neural Crest Stem Cells; CACs: Circulating Angiogenic Cells; EPCs: Endothelial Progenitor Cells

## Introduction

Penile erection is a neurovascular phenomenon controlled by the hypothalamus and the sympathetic and parasympathetic neurons [1]. Erectile Dysfunction (ED) is the persistent inability to initiate or maintain erection for sexual activity. It is commonly associated with aging and is also caused as a result of various metabolic conditions, such as diabetes, hypertension, atherosclerosis, and hypercholesterolemia, or mechanical manipulations such as in trauma or surgery [2]. Aging affects vasoconstriction, nerve-mediated relaxation, and Reactive Oxygen Species (ROS) production; a series of such processes can result in tissue damage [3,4]. Diabetes induces neuropathic damage associated with ED [5]. ED is also caused due to the impairment of nitric oxide-mediated endothelium relaxation in hypercholesterolemia [6,7]. In addition, various neurological diseases, such as Parkinson's disease, or neurological trauma, such as spinal cord injury and cavernous nerve injury, also affect penile erection [8]. ED caused due to damage to the nerves associated with erectile function is referred to as neurogenic ED.

Stem cells have the potential to regenerate and restore normal function in cells after injury or degradation. In addition, they can differentiate into cells of various lineages [9]. Stem cells can repair damaged tissues both by direct regeneration and by a paracrine effect causing the secretion of combinations of trophic factors [10]. Hence, they have been hypothesized to have therapeutic effects in various diseases. Stem cell technologies have been used to study smooth muscle and endothelial cell repair in ED.

The selection of the animal model is an important factor in studies on neurological disorders. Commercially available transgenic mice and animal models of chemically induced neurological disorders have been used in previous studies [11-13]. Aging animals are a natural model for ED, and the animal model of type I diabetes has been developed in the past by intraperitoneally injecting streptozotocin to induce β cell destruction [14]. In this case, both young (approximately 5 month old) and aged rat (about 13-20 month old) were used for one experiment [15].

In this review, we focus on the potential application of stem cell therapies for neurogenic ED.

## Embryonic Stem Cells

Embryonic Stem Cells (ESCs) are totipotent cells that can differentiate into cells of all lineages. They have enormous biological potential for the treatment of various diseases. In one study, Neural Embryonic Stem Cells (NESs) differentiated from rat ESCs were injected into the major pelvic ganglion of rat models of cavernosal nerve injury [16]. The stem cell-injected rats showed improved intracavernosal pressure and neurofilament expression. These results suggested that NES scan be used to improve erectile function in rats with cavernosal nerve injury. However, the use of ESCs is limited because of ethical concerns [7].

## Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) can differentiate into various cell types, including osteoblasts, chondrocytes, myocytes, adipocytes, and neurons [17]. All MSCs, including bone marrow derived MSCs (BM-MSCs), skeletal muscle-derived stem cells (MDSCs), and Adipose-derived stem cells (ASCs) exhibit similar biological properties and therapeutic capabilities.

ASC sare pluripotent cells that can be easily obtained by liposuction. They are capable of differentiating into neuron-like cells, smooth muscle cells, and endothelial cells *in- vitro*. In a previous study, ASCs were injected into the bladder and urethra in rat and mouse models of immunodeficiency, such as Rnu athymic rats and severe combined immunodeficiency mice [18]. These ASCs survived up to 12 weeks in the lower urinary tract and differentiated into smooth muscle cells. These results suggested that ASCs may be a




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useful and cost-effective source of stem cells for urinary tract studies. In another study, ASCs were injected into the penis in type 2 diabetic rat models [19]. It was found that although only a small number of ASCs proliferated, the parameters of erectile functions, such as the Intra Cavernous Pressure (ICP), the expression of neuronal nitric oxide synthase, and the number of endothelial cells, improved in the ASC-injected rats.

Recently, ASCs and ASC-derived lysates have also been used in rat models of cavernous nerve crush injury [20]. Both ASCs and the lysates improved erectile function and smooth muscle content in the rats; they also alleviated fibrosis. In particular, as ASC-derived lysates were also shown to improve erectile function, it was hypothesized that intracellular and/or secreted biomolecules from ASCs may have a therapeutic effect in ED [21].

The transplantation of BM-MSCs into the skeletal muscles of the hind limbs of rats with streptozotocin (STZ)-induced diabetes has been shown to increase the expression of Vascular Endothelial Growth Factor (VEGF) and basic fibroblast growth factor [22]. In addition, parameters of physiological activity, such as nerve conduction velocity, sciatic nerve blood flow, and capillary number-to-muscle fiber ratio, were found to improve in the MSC-injected diabetic rats. Hence, we hypothesize that MSCs can be used in the future for stem-cell–based therapies in ED.

MDSCs have the potential to restore urethral function [23]. MDSCs were transplanted into rats in which both sciatic nerves were transected-the animal model of urinary incontinence. The MDSC-transplanted rats showed increased leak point pressure and improve durethral muscle strip contractility, but not urinary retention.

Another study showed that MSDCs can be used to restore penile innervation and improve erectile function impaired due to nerve injury [24]. MDSCs were transplanted into the penisin rat models of erectile dysfunction induced by bilateral cavernous nerve injury. The ICP at 2 and 4 weeks after surgery was found to be improved in the MDSC-injected rats.

Further, it is believed that skeletal MDSCs can be used as therapeutic tools for aging-related ED. Skeletal MDSCs transplanted into the corpora cavernosa of young and aged rats proliferate and differentiate into smooth muscle cells [15]. The improvement in the function of the cavernosal nerve after electrical field stimulation was similar in aged and young rats.

## Neural Crest Stem Cells

Neural Crest Stem Cells (NCSCs) are derived from the dorsal part of the neural tube and migrate to different locations during development. They can differentiate into various cell types, including peripheral neurons, glia (Schwann cells), melanocytes, endocrine cells, smooth muscle, skeletal muscles, and bone cells [25].

Immortalized human NCSCs, when transplanted into the cavernosum of adult rats, have been shown to differentiate into endothelial and smooth muscle cells expressing cell specific markers 2 weeks after transplantation [2]. These NCSCs could regenerate endothelial and smooth muscle cells in the corpus cavernosum; hence, they may have therapeutic applications for ED.

## Endothelial Cells

Human serum inhibits the differentiation of Circulating Angiogenic Cells (CACs) into circulating Mono Nuclear Cells (MNCs) and Colony-Forming Units (CFUs). Further, serum from ED patients was found to have a strikingly greater ability to inhibit this differentiation than serum from healthy men [26]. Since the number of circulating progenitor cells is reduced in patients with cardiovascular risk factors [27] and since ED is associated with endothelial damage and dysfunction, these results suggested that maintaining vascular homeostasis is important for treating these patients. Bone marrow-derived Endothelial Progenitor Cells (EPCs) therefore have therapeutic potential in ED because they can enter peripheral circulation and promote endothelial repair.

Gou et al., transplanted VEGF-expressing EPCsin the corpora cavernosa of diabetic rats and found that the transplanted EPCs survived and differentiated into endothelial cells in the VEGF-induced neovascularized region of the diabetic rats. ICP increased significantly in the EPC-transplanted rats, indicating ED restoration [28].

These results suggested that reduce endothelial damagein ED.

## Conclusion

ED is a secondary symptom in various diseases. Stem-cell–based therapies show promise as useful and safe tools for the treatment of ED in the near future.

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