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Stem Cell Therapy for Male Urinary Incontinence

Key Words

Urinary incontinence · Prostatectomy · Adult stem cell ·
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Abstract

Introduction: Among the medical and surgical options which have been proposed in the last years for the management of male stress urinary incontinence (SUI), stem cell therapy represents a new frontier treatment. The aim of this paper is to update the current status of stem cell therapy in animal and human studies for the management of iatrogenic male SUI. **Material and Methods:** A PubMed review of the literature on stem cell therapy for the treatment of male SUI was performed. **Results:** Regarding animal studies, bone marrow-, muscle- and adipose-derived stem cells have been widely studied, showing regeneration of the urethral sphincter and recovery of the damaged pelvic nerves. With regard to human studies, only four papers are available in the literature using muscle- and adipose-derived stem cells which reported a significant improvement in sphincteric function and incontinence with no severe side effects. **Conclusions:** In spite of these promising results, further studies are needed with longer follow-ups and larger numbers of patients in order to clarify the potential role of stem cell therapy for the treatment of male SUI.

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Introduction

Male stress urinary incontinence (SUI) affects a substantial number of patients after prostatic surgery, with an incidence which varies dramatically between 0.8 and 87%, and remains a critical determinant in postoperative health-related quality of life [1–6]. Initial management of SUI is generally based on pelvic floor muscle training, biofeedback or electrical stimulation [7, 8]. A low evidence level is reported in the literature regarding the administration of duloxetine or anticholinergic drugs in cases of mixed incontinence [9, 10].

When conservative and pharmacologic managements fail, surgical therapy of SUI becomes inevitable. Injectable bulking agents are minimally invasive but have a poor long-term efficacy [11, 12]. More invasive approaches, like sling procedures or artificial urinary sphincter implantation, are more effective but have a higher morbidity [13–15]. In this setting, there is an increasing need for minimally invasive and effective approaches with low morbidity for the treatment of SUI.

Stem cells represent a self-renewing population of cells derived from healthy tissue which can be differentiated into a variety of other cells. The ideal strategy for curing SUI using stem cell therapy would allow for the regeneration of functional periurethral tissue to provide adequate mucosal coaptation and to restore resting urethral closure pressures [16].

Multiple animal models have been used to study the effect of stem cells in tissue regeneration of the urethra and, more recently, some human trials have also been conducted. The aim of this paper is to update the current status of stem cell therapy in animal and human studies for the treatment of male SUI.

Stem Cell Therapy

Embryonic stem cells are pluripotent cells obtained from the inner cell cluster of blastocytes. They have the potential to differentiate in vitro into cells from all three embryonic germ layers. In order to avoid ethical and political problems which could limit the use of these cells, research into alternative therapies for SUI has focused on the use of autologous adult-derived stem cells. Unfortunately, adult stem cells are not immortal and have a more limited differentiation potential. Investigations into the use of stem cells for the treatment of SUI have focused on mesenchymal-derived stem cells. These cells can be isolated from many different sources such as bone marrow, muscle, adipose tissue, liver tissue, amniotic fluid, placenta, umbilical cord and dental pulp [16]. Table 1 summarizes the main animal studies which have been conducted in the last years using adult stem cells [17–26].

Animal Studies

Bone Marrow-Derived Stem Cells (BMSCs)

Of all the mesenchymal stem cells, BMSCs have been most widely studied for the regeneration of many muscular structures. With regard to the regeneration of urethral sphincter, histological and immunohistochemistry evaluation demonstrated the differentiation of autologous BMSCs into striated muscle cells and peripheral nerve cells [17, 18].

Muscle-Derived Stem Cells (MDSCs)

MDSCs are quiescent satellite cells found in myofibers that can proliferate to form myoblast and, eventually, form myotubes and new muscle tissue [20]. Other studies have shown the power of MDSCs to restore muscular contraction of the muscular sphincter and to recover the damaged pelvic nerves [21, 22]. It has also been suggested that the formation of myotubes may activate intrinsic nerve regeneration and formation of the neuromuscular junction [23, 27, 28]. Furthermore, studies on the pig model showed an increase in urethral pressure profile and muscular myofibrils after injection of MDSCs into the striated urinary sphincter [24].

Adipose-Derived Stem Cells (ADSCs)

ADSCs can differentiate into fibroblasts, myoblasts, smooth muscle cells, endothelial cells or neurogenic cells [29]. With regard to the treatment of SUI, ADSCs are of special interest for mesodermal and neuronal regeneration and to promote revascularization. In fact, neural-dif-

Table 1. Main animal studies reported in the literature concerning adult stem cell injection for the treatment of SUI

Reference (first author)	Stem cell source	Species	Target organ	Follow-up
Drost [17]	BMSCs	rat	bladder	4 weeks
Kinebuchi [18]	BMSCs	rat	urethra	13 weeks
Kanematsu [19]	BMSCs	rat	bladder	12 weeks
Chancellor [20]	MDSCs	rat	urethra, bladder	3–4 days
Cannon [21]	MDSCs	rat	urethra	2 weeks
Kwon [22]	MDSCs	rat	urethra	4 weeks
Hoshi [23]	MDSCs	rat	urethra	12 weeks
Mitterberger [24]	MDSCs	pig	urethra	3 weeks
Lin [26]	ADSCs	rat	urethra	4 weeks
Zeng [30]	ADSCs	rat	urethra	12 weeks

Table 2. Main human studies reported in the literature concerning adult stem cell injection for the treatment of male SUI

Reference (first author)	Stem cell source	Species	Number of patients	Harvesting tissue	Target organ	Follow-up
Strasser [31]	MDSCs	human	63 (42 men/21 women)	biceps muscle	urethra	12 weeks
Mitterberger [34]	MDSCs	human	63 (men)	biceps muscle	urethra	12 months
Yamamoto [35]	ADSCs	human	2 (men)	anterior abdominal wall	urethra	3 months
Yamamoto [37]	ADSCs	human	3 (men)	anterior abdominal wall	urethra	6 months

differentiated ADSCs present glial characteristics and promote nerve regeneration, as observed after transplantation in rat models [30]. Furthermore, periurethral injection of ADSCs exhibited in vivo differentiation into smooth muscle cells and improved urethral resistance [25, 26].

Human Studies

Very few studies are reported in the literature using autologous adult-derived stem cells for the treatment of SUI in human patients (table 2). Furthermore, even fewer papers have been published concerning male SUI. The first experience was reported by Strasser et al. [31] in 2007 after treating a group of men and women affected by SUI with ultrasound-guided injection of myoblasts and fibroblasts into the rhabdosphincter and submucosa, respectively. After a follow-up of 12 months, the authors assessed a significant improvement of the incontinence and quality of life scores, the thickness of urethra and rhabdosphincter and the contractility of the rhabdosphincter. These postoperative changes were explained by the formation of new muscle tissue in the rhabdosphincter [31, 32]. No severe side effects were reported. With regard to gender, postoperative results were better in women than in men. This aspect has been related to the more difficult injection of MDSCs in men than in women due to different male anatomy of the urethra and the postoperative scarrings after surgery. Unfortunately, these published results have been retracted due to deficiencies in obtaining patients' consents, protocol irregularities, and a missing ethical committee approval [33]. However, these outcomes were substantially confirmed in 2008 when the same group reported a more extended experience with a longer follow-up using the same technique on 63 male patients with SUI after radical prostatectomy. In fact, a significant postoperative improvement of incontinence and quality of life scores as well as thickness and contractility of the rhabdosphincter with no severe side effects were reassessed at 1 year of follow up. Preoperative strictures, scars and fibrotic areas in the membranous urethra, prior injection of bulking agents or internal urethrotomy as well as radiation therapy negatively influenced the success rates. These data strongly supported the experimental findings that the ultrasound-guided injection of MDSCs leads to regeneration of the urethral submucosa and the rhabdosphincter and not to passive obstruction on the lower urinary tract [34].

More recently, in 2010, Yamamoto et al. [35] reported their preliminary experience concerning the periurethral

injection of ADSCs in 2 patients with SUI after radical prostatectomy. Unfortunately, this study was also retracted due to the unintended breach of established ethical guidelines [36]. However, in 2012, the same authors published the outcomes regarding the initial 3 cases using the same procedure and reported a progressive improvement of the sphincteric function, which was shown by an increase of the maximum urethral closing pressure and functional profile length, as well as a decreased leakage volume assessed by a 24-hour pad test with no significant adverse events [37].

These few promising clinical results require further evaluation in order to validate results, determine durability and focus on safety and possible adverse reactions.

Conclusions

Although the aforementioned animal and human studies have shown promising results, suggesting a potential role for adult-derived stem cells in the treatment of SUI, further research with longer follow-ups and larger numbers of patients needs to be conducted in order to understand the real mechanism of action and the long-term safety of these cells. If these aspects are confirmed, cell therapy will probably be proposed as a standard treatment for SUI in the future.

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