Stem Cell Therapy for Male Urinary Incontinence

**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 po-
litical 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. Unfortu-
nately, 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 iso-
lated from many different sources such as bone marrow,
muscle, adipose tissue, liver tissue, amniotic fluid, pla-
centa, umbilical cord and dental pulp [16]. Table 1 sum-
maries the main animal studies which have been con-
ducted 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 muscu-
lar structures. With regard to the regeneration of urethral
sphincter, histological and immunohistochemistry eval-
uation 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 tissue 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 regenera-
tion and to promote revascularization. In fact, neural-dif-

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

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

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

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

**Acknowledgement**

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**References**


