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Stem Cells for Urinary Incontinence: Functional Differentiation or Cytokine Effects?

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Abstract

Minimally-invasive stem cell therapy for stress urinary incontinence may provide an effective nonsurgical treatment for this common condition. Clinical trials of periurethral stem cell injection have been underway and basic science research has demonstrated the efficacy of both local and systemic stem cell therapies. Results differ as to whether stem cells have a therapeutic effect by differentiating into permanent, functional tissues, or whether they exert benefits through a transient presence and the secretion of regenerative factors. This review explores the fate of therapeutic stem cells for stress urinary incontinence and how this may relate to their mechanism of action.

Keywords

Cell Differentiation; Cytokines; Stem Cells; Urinary Incontinence; Urology; Regenerative Medicine

Introduction

Urinary incontinence afflicts up to 1 in 2 women.[1] It poses significant economic and quality of life burdens, with over $32 billion annual U.S. dollars spent managing it.[2] Stress urinary incontinence (SUI) impacts up to 1 in 4 women and accounts for over $12 billion annual U.S. dollars in health care costs.[1] Incontinence imparts major psychosocial burdens on those afflicted by it, and places women at risk for other debilitating conditions, including

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depression, anxiety, low self-esteem, social isolation, infection, pain, and sexual dysfunction.[3] Therefore, a clear need to develop cost-effective, durable, and minimally invasive treatment for the condition exists.

Some patients with SUI effectively respond to conservative treatment, including pelvic floor physical therapy, biofeedback, pelvic floor electrical stimulation, or continence devices, such as pessaries.[4, 5] Several surgical and transurethral treatments are also available, including peri-urethral bulking injections and sub-urethral slings, which are the gold standard therapy for the condition.[6] Slings offer the highest long-term cure rate for SUI, but like any surgery, are not without complications, which include sling erosion, urinary retention, bladder perforation, wound issues, and pain.[7] Moreover, reports of complications involving vaginal mesh, while not pertaining to mid-urethral slings, have negatively swayed public opinion about such procedures.[8] To date, besides conservative treatments, injectable therapies used to coapt the urethral lumen remain the least invasive SUI treatments providing some clinical benefit. These interventions produce no visible scars, but have largely fallen from clinical favor due to limited durability and efficacy.[9]

The utilization of stem cells and other progenitor cells as injectable agents, via a similar approach as bulking agents, present potential alternate therapies. Stem cells are unique due to their ability to proliferate, self-renew, and produce a population of differentiated progeny, making them a promising therapy in the field of regenerative medicine. To date, stem cells have been classified into four main categories. Embryonic stem cells (ESCs) derived from human blastocysts represent the most undifferentiated form, possessing the ability to differentiate into any human cell type.[10] Theoretically, they provide the greatest therapeutic potential but their use is restricted by ethical concerns, as well as potential allogenicity and tumor oncogenesis.[11] Amniotic fluid-derived stem cells (AFSCs) are a second form. This heterogeneous cell population is isolated from the amniotic fluid or placental membrane of a developing fetus, but their proliferation potential is only intermediate along the stem cell spectrum. Like ESCs, AFSCs can differentiate into many different cell lineages, but they are felt to possess lower tumorigenicity.[12] A third form are differentiated, somatic cells that are “reprogrammed” into pluripotent cells.[13] These induced pluripotent stem cells (IPSCs) possess similar differentiation potential to ESCs but preclude the necessity of an embryo. The utility of IPSCs in regenerative urology requires further investigation. Lastly, adult stem cells (ASCs) represent the most well understood type. These are tissue-specific progenitor cells, which are the most limited on the spectrum of differentiation.[14] Mesenchymal stem cells (MSCs) are a subset of ASCs that can be isolated from bone marrow and induced to differentiate into various cell lineages. Recently, alternative sources of ASCs, such as muscle-derived stem cells (MDSCs) and adipose-derived stem cells (ADSCs) have been obtained with less invasive techniques compared to MSCs.[15]

In the pre-clinical setting, a variety of SUI models exist for investigating pathophysiology and treatment.[19, 20] Leak point pressure (LPP), a measure of urethral resistance to leakage, determined by measuring bladder pressure at the time of leak, is a frequently utilized surrogate for SUI. Methods to decrease urethral resistance in order to elicit SUI are numerous and include direct urethral injury, urethrolysis, pudendal nerve injury, and vaginal distension.[21–26] Bladder pressure can be increased to induce leakage using direct bladder

compression, sneeze testing, or direct infusion using a suprapubic catheter.[26–28] Additional assessments of these models include measurement of urethral closure pressure, testing of EUS function via electromyography (EMG), and histological studies of the EUS investigating muscle content and organization.[19]

This review addresses various applications of stem cells and progenitor cells to SUI, with a focus on recent developments in the field. The article also gives specific consideration to the mechanisms of therapeutic benefit from such cells, as well as implications for future studies and clinical applications. Commentary on the economic aspects of regenerative therapy for SUI is also included.

Clinical Trials of Stem Cell Therapy for Stress Urinary Incontinence

A North American trial of autologous MDSCs for SUI has assessed outcomes at 3 time points. A 1 year follow-up found most women experienced improvements in SUI after transurethral sphincteric injection of autologous MDSCs from an extremity skeletal muscle biopsy.[16] Subsequently, it was found that high dose (32–128 million cells) performed better than low dose (1– 10 million cells) treatment 12 months after injection, conferring a nearly 89% rate of 50% incontinence pad weight reduction and 78% rate of 50% fewer leaks.[29] Some patients received repeat treatment and obtained additional benefit. An analysis of safety and efficacy found no significant adverse events and that both objective (voiding diary and pad weight) and subjective (questionnaire) outcomes improved in some women.[30] The only adverse events were discomfort and bruising at the biopsy or injection sites.[29] This group has since conducted a multicenter, randomized, double-blind, placebo controlled study to determine clinical efficacy in treating SUI. Their complete data has not been published, but initial results suggest the treatment is safe and may have a durable effect on incontinence events after 2 years of follow up. However, a major limitation of this trial was a high placebo responder rate, which halted enrollment at 61% of the planned study size, and required post hoc adjustment of the endpoints to achieve a treatment effect.[31]

A similar study of transurethrally-injected MDSCs was conducted in Poland on a cohort of 16 women with SUI.[17] The mean number of injected cells was relatively small (approximately 6 million) compared to the American trial, but they were still able to report a 75% success rate and 50% cure rate 2 years after a single treatment. Specifically, 8 of the 16 patients achieved full continence, with no urine loss or pad use, full control of urination, and no loss of urine during valsalva. Four of the 16 patients had improved continence with decreased daily pad use, and most continued to have stress incontinence with valsalva. The rest of the cohort showed no improvement in symptoms, and two of the patients went on to have surgical intervention. No serious adverse events or complications were observed with either the muscle biopsy or stem cell injection. Quality of life was significantly improved compared to pre-injection in a majority of these patients up to 4 years after intervention.[32]

Sèbe et. al investigated the use of transurethral injections of autologous MDSCs in patients with severe SUI who had scarred, fixed urethras and had failed previous surgical management. Even in this difficult population, 3 of 12 patients were dry after 12 months (0 to 3 leaks weekly and a 5g decrease from baseline on the 1 hour pad test), a majority showed

objective improvement, and half had improved quality of life scores.[18] After 6 years of follow up, 2 of the patients in the “dry” group remained dry, while most of the patients that showed partial improvement had regressed.[33] Together, these results show that some patients respond to treatment, repeated treatments benefit certain cases, and there is potential for a durable effect in even the most complicated cases. The factors that predict these outcomes are unclear, but the question of the fate of injected cells comes to mind. In less successful cases, did the cells not engraft and differentiate into functional muscle? Why did certain cases not show durable benefit?

A Slovenian study added 5-weeks of transvaginal electrical stimulation before and after injection to bolster cell engraftment.[34, 35] Myoblasts, which are MDSC progenitor cells and myogenic precursors, were isolated from extremity skeletal muscle and injected under ultrasound guidance into 2 layers around the EUS.[34, 35] Following the procedure, patients self-administered transvaginal electrical stimulation at home for 5 weeks. At 6-week follow up, 29 patients (78.4%) had a negative stress test and reported their incontinence improved, while 5 patients reported cure. These results persisted and even improved at 6 month follow up, with nearly 24% cure and 53% improvement rates. Additionally, 95% of patients would recommend the treatment to others, suggesting a high satisfaction rate.[34, 35] One limitation of this study was the lack of a control group to delineate the effects of electrical stimulation on the native and transplanted cells. However, as shown in other studies, electrical stimulation can upregulate homing cytokines to aid stem cell engraftment or alter the function of transplanted cells.[36] The overall rate of improvement was similar to the North American trial, even with the addition of electrical stimulation. With the differing methods, a comparison with and without electrical stimulation is warranted.

A Finnish study achieved comparable outcomes with autologous adipose-derived cells suspended in a bovine collagen and saline mixture for transurethral intrasphincteric injection.[37] Outcomes improved over time when assessed 3, 6, and 12 months following treatment. By 1 year, 60% of subjects had negative cough (leak) tests but only 40% were satisfied, despite a 100% rate of decreased pad weights and subjective improvement.[37] This study was limited by a small sample size of 5 patients and lack of a collagen-only control group. Collagen, once a popular injectable urethral bulking agent, theoretically reduced leakage via a bulking effect while the cells engrafted. Interestingly, a study in Denmark investigated minced autologous skeletal muscle injected peri-urethrally with ultrasound guidance immediately after biopsy. One year later women with uncomplicated incontinence had 25% cure and 63% improvement rates, relatively consistent with these other studies.[38] This latter study suggests either the skeletal muscle precursor cells in the minced tissues provided benefit, or the suspended myocytes engrafted.

Collectively, clinical trials of stem cells for SUI succeeded in most of patients, but not all. Some subjects found transient benefit, while others achieved durable results. An unfortunate limitation of clinical trials is an unknown fate of the injected cells. Biopsy of the urethral sphincter is not safe and not without side effects, while viral or genetic labeling of cells is unethical in the absence of proven safety. Thus, clinical trials, while promising, leave many questions unanswered. Laboratory studies, however, can shed light onto the fate of therapeutically injected cells and their mechanisms of therapeutic action.

Laboratory Studies of Undifferentiated Stem Cells

Major benefits of laboratory studies of stem cells in SUI models are the ability to determine their fate and their effects on tissues. One such study analyzed human MSCs in an uninjured male rat model.[39] After injection into the peri-urethral pelvic floor musculature, the cells survived at least 4 months, migrating towards regional muscle fibers and localizing towards neuromuscular endplates. However, little cell proliferation occurred and any that did, decreased with time.[39] A more recent study analyzed rabbit ADSCs in a mouse vaginal distention SUI model.[40] The cells were injected vaginally 1 hour after injury and decreased in number over 3 weeks. However, some cells remained up to 8 weeks.[40]

Cells were not seen to migrate to other organs. This study would have benefited from a non-injured control group injected with labeled ADSCs in order to study the effect of the stem cells in the absence of tissue injury. In both studies, the decline in transplanted cell numbers and reduction in proliferation over time suggests cells are only transiently present. This may explain some of the variability in humans, although clinical trials generally found increasing response rates with time from treatment, which may suggest a trophic or slow innate regenerative response initiated by the cells.

Functional studies of local injection of undifferentiated stem cells have provided insight into their mechanism of action. Chermansky et al. studied the effect of MDSCs on LPP in a rat model of intrinsic sphincter deficiency (ISD).[41] Experimental animals underwent urethrolysis followed by periurethral injection of labeled MDSCs. Control animals were injected with a saline solution, and another group underwent a sham operation. Rats treated with MDSCs showed significant increases in LPP compared to controls at 2, 4, and 6 weeks after injection. Histologic analysis revealed that the stem cells had integrated within the striated muscle fibers at the site on injury, and there was also increased neural proliferation in the MDSC group.

Another study in rats utilized sub-mucosal bladder neck and urethral injections of stem cells or muscle-differentiated precursor cells suspended in biocompatible gel 2 weeks after bilateral transection of the pudendal nerve and nerve to the levator ani. Control groups included gel injected alone or no treatment. Four and 8 weeks after injection, LPP was significantly higher in all treatment groups compared to controls, and vascular ingrowth, as well as viable cells, were noted in groups given cells.[42]

The authors concluded that stem cells or muscle-differentiated cells could survive and grow to promote angiogenesis, but further studies are needed to discern whether these stem cells could differentiate into myoblasts.

Similarly, improved sphincter function after injury occurred in treated groups of female rats that underwent bilateral pudendal nerve excision before muscle-derived stem cell injection into the bladder neck and proximal urethra, although timing of treatment after injury was not specified.[43] A rabbit model of cryoinjured internal urethral sphincter and bladder neck was used to compare labeled ADSC treatment with cell-free media given via transvesical injection 1 week after injury.[44] Fourteen days after injection, LPP was significantly increased with ADSC treatment, and histological assessment revealed ADSCs stained

positive for myoglobin, SMA and Pax7 antibodies (markers for skeletal muscle, smooth muscle, and myoblasts, respectively). Markers of neural and vascular cell phenotypes were also observed.[44] Together, these studies suggest improvements in LPP may result from integration of stem cells into injured tissue and differentiation into distinct cell lineages to provide a theurapeutic benefit.

In contrast, other studies of local stem cell treatments have shown therapeutic benefits with only transiently present cells. A mouse model of bilateral pudendal nerve transection given either labeled human AFSCs or Plasma-Lyte via periurethral injection 1 week after injury was compared to sham injured animals.[45] Two and 4 weeks after treatment, LPP was significantly increased with stem cell treatment compared to treatment with plasma solution, although there were no significant differences 1 week after injury. While the cells differentiated and expressed neural phenotypes near EUS neuromuscular junctions, they were only visualized periurethrally 3 days after injection, with decreased signal at 7 days, and no signal 10 or 14 days after injection.[45]

Similarly, in a vaginal distention model using rats, human MSCs given periurethrally immediately after injury were compared to dermofibroblasts, saline, and uninjured controls, with a separate but similar assessment of the same treatments via intravenous systemic administration in different animals.[46] Saline and dermofibroblast-treated animals had significantly lower LPPs than non-injured controls at days 4 and 14. LPP was not significantly reduced in the stem cell treated groups 4 days after treatment, an effect which persisted to 10 and 14 days, regardless of treatment route. Histological analyses showed increased connective tissue and vascular density in the stem cell groups, even though the cells were only transiently present. Stem cells were not visualized in urethras 4, 10, or 14 days after systemic or local injection, however they were present 2 days after local injection. These results demonstrate that a durable functional benefit may be achieved with stem cell treatment despite the apparent early disappearance of the cells and their progeny. Taken together, these data seem to refute the theory that stem cells act by engrafting and differentiating into peri-urethral tissue.

Whether isolated stem cells differentiate into mature and functional tissues, or remain at the site of injection only transiently, they appear to benefit urinary function. This raises the question of the mechanism of action provided by stem cell therapy. One possibility is that the physical bulking of the urethra results in LPP gains in the short term, as demonstrated in a study comparing several cell types injected in gel suspensions.[42] It can be argued that this effect is negligible for cells suspended in thin solutions, such as saline. A recent German study further investigated this question using high-definition urethral pressure profilometry on Göttingen minipigs.[47] The authors showed that injections of MSC-containing isotonic fluid up to 1ml did not change urethral wall pressures compared to sham-treated animals after up to 12 months of follow up. They concluded that peri-urethral injections of cells in clinically applicable aliquots (1 ml) do not provide a non-specific bulking effect to the urethra. To this point, comparisons between human MSCs and dermofibroblasts suggest improved LPP comes from something more than just their bulking effect.[46] The relatively brief presence of the cells in this study further suggests their effect is not engraftment and function, but rather an influence on the local environment and recovery from injury. There is

a growing body of evidence in the stem cell literature that supports this paracrine hypothesis, whereby the therapeutic effects of the cells are due to secretion of soluble factors such as cytokines, chemokines, and growth factors that may potentiate tissue repair. [48–50]

Laboratory Studies of Differentiated Stem Cells

Along with the study of undifferentiated stem cells, other work focused upon utilizing differentiated precursor cells derived by steering stem cells into specific lineages. Human ESCs and IPSCs from 2 different fibroblast lines were differentiated into smooth muscle precursor cells (pSMCs) and used in a rat model of SUI consisting of ovariectomy and urethrolysis.[51] Three weeks following complete urethrolysis, pSMCs from both cell lines were injected periurethrally. Bladder smooth muscle cells were injected periurethrally in other injured animals to provide treatment controls.[51] Significantly greater LPP recovery occurred with smooth muscle precursors from the induced pluripotent cell line, as well as bladder smooth muscle cells, but not with human embryonic-derived cells.[51] However, sphincter function recovery, as measured with EMG, was significantly greater with human-derived cells and bladder cells, compared to either induced lineage.[51] Cells remained near injection sites initially but disappeared 9 days later, while their functional benefits persisted for 5 weeks.[51] Subsequent histological analyses showed increased elastin and collagen III in the urethral tissues of treated animals in the absence of human gene expression, suggesting that the cells induced native tissue remodeling.[52] Thus, similar to undifferentiated cells, differentiated cells appear to improve recovery in SUI, even in the absence of engraftment.

In similar work, human AFSCs were differentiated into muscle, neuronal, and endothelial progenitor cells for injection into denervated urethral sphincters of mice.[53] The timing of treatment after injury was not specified; however, differing combinations of cell types significantly improved LPP both 2 and 4 weeks post-treatment, relative to a saline control.[53] Histological analyses found varying degrees of new muscle fibers and neuromuscular junctions in all cellular treatment groups.[53] The authors were able to visualize, *in vivo*, the early-differentiated stem cells up to 14 days after injection. Likewise, in a primate model with pudendal nerve cauterization and transection, durable (up to 12 months) increases in urethral pressure and amounts of sphincter muscle, with decreased sphincter fibrosis, occurred after GFP-labeled skeletal muscle precursor cell injection compared to controls.[54] Treatment was administered 6 weeks after injury. Histology confirmed cell survival in skeletal muscle layers and blood vessels up to 3 months.[54] In contrast to other work with transiently present partially differentiated precursor cells, these studies may suggest a mechanism of improved recovery through engraftment and new (possibly functional) tissue development.

Considering discrepant results from studies of partially differentiated stem cells, the need for identifying their mechanism of action is clear. Based upon the studies presented, some investigations clearly demonstrate viable labeled cells that matured into functional tissue types long after injection, while others show cells are only transiently present despite significant and durable benefits to recovery. Considering this, the possibility that cells may work through more than engraftment, proliferation, and differentiation is reasonable – some cells may act by altering the local environment to facilitate recovery during a brief residence,

while others may not only influence the local environment, but also engraft and mature to supplement tissue function.

Laboratory Studies of Systemic and Acellular Regenerative Therapies

Injury related to childbirth upregulates stem cell homing cytokines in the pelvic organs of rats.[56–58] A vaginal distention simulated childbirth model tested the ability of intravenous MSCs to home to injury sites.[59] Cells given intravenously 1 hour after injury were tracked and found to preferentially home to injured pelvic organs. Microscopic analysis further confirmed this, as did quantitative assessment with flow cytometry.[59] In a follow-up study, intravenous stem cell administration was shown to have superior functional and anatomic recovery compared to saline.[60] LPP recovered only in the stem cell group, with injected cells observed in the urethra and vagina, along with increased elastin fiber density and less smooth muscle disruption relative to controls. EUS activity as measured by EMG was not significantly different, which suggests the cells aided continence recovery through their effects on tissue quality, as noted in elastin and smooth muscle differences.

Another arm in this study received the same injury but was given periurethrally injected concentrated conditioned media (filtered and concentrated culture media in which the stem cells were grown, containing secretions of the cells but not the cells themselves) or standard concentrated culture media (never exposed to cells) as a control. Similar results were observed, with significantly impaired LPP in the control group but not in the group given concentrated conditioned media containing the cytokines secreted by the stem cells.[60] Similar histologic findings occurred and no difference in EUS EMG was also observed. A follow-up study was done with bilateral pudendal nerve crush added to the vaginal distention and intravenous stem cells compared to saline or intraperitoneal concentrated conditioned media compared to control media. Again, LPP recovery was significantly impaired with saline or control media treatment, but not systemic stem cells or conditioned culture media – this time also systemically administered.[61] Improved elastic fiber density was again confirmed, as was reduction in the pathologic changes in pudendal nerve fascicles.[61] Electrophysiological analysis of pudendal nerve activity mirrored that of LPP with significantly impaired recovery after saline or control media treatment but not stem cells or conditioned culture media.[61] These studies provide strong evidence that stem cell treatment for SUI may not require cellular engraftment and differentiation, but rather cytokine effects that are as effective systemically as they are locally.

Stem cell conditioned media has been shown to benefit cardiac repair and prevent kidney injury in various animal models.[62, 63] Investigating the nature of stem cell secretions, or the “secretome”, is currently an exciting area of research. Characterization of the secretome has largely involved proteomic analysis, and a myriad of gene products involved in vascularization, metabolism, immune response, and tissue differentiation have been confirmed.[64, 65] Countless signaling pathways have been proposed, and it appears that the paracrine factors may be released in a differential fashion depending on the local microenvironment after injury.[49] Further research is required to investigate the mechanisms by which acellular stem cell therapies exert their effect in SUI.

Discussion

Whether undifferentiated, partially differentiated, or acellular, regenerative therapies to treat stress urinary incontinence have shown promising results with little apparent morbidity.[29] Clinical trials continue to show benefit in some patients. Laboratory studies confirm that cells at various points along the differentiation pathway, and from various sources, can be utilized. Additionally, new evidence suggests the therapeutic benefit may even be provided with acellular interventions, possibly explaining the findings in many pre-clinical studies of improved recovery with only transiently present stem cells. Moving forward, working toward understanding why certain patients respond to treatment and others do not is an area of need. Otherwise, the development of acellular treatments that provide the benefits of stem cells remains a significant opportunity.

From an economic perspective, SUI is a significant issue. The use of regenerative therapies to treat the condition seems feasible. Current clinical trials utilizing muscle biopsies to generate injectable cells require the tissue obtained in the clinic be sent to a centralized laboratory for processing and growth of the colony of cells. This requires time, careful handling of materials, and the preservation of living cells. The costs associated with this are not insignificant, considering the necessary safeguards for protecting against complications like loss of cell viability, infection, or receiving another person's cells. While the use of allogenic stem cells has succeeded in the pre-clinical setting with established colonies of donor cells from one animal used to treat another, this approach raises challenges in the clinical arena regarding cell compatibility. Considering these limitations, acellular regenerative therapies may offer a more economically and logistically feasible option for SUI treatment. Specifically, providing the benefit of stem cells without the need to transport, handle, and inject living cells offers the advantages of easier transport of the therapeutic agent and a theoretically lower biologic risk to those handling it. Furthermore, the production of acellular stem cell factors for injection can be accomplished using established and self-renewing colonies of cells, enabling the process to be scaled up, allowing the agent to be made in large quantities. Utilizing acellular regenerative therapies from allogenic sources has significant therapeutic and economic potential, assuming the agent can be produced and filtered to ensure its immunologic compatibility with multiple recipients.

Significant opportunity exists for developing regenerative therapies for SUI treatment. The recently published 2017 American Urological Association and Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction guidelines for SUI states "stem cell injection for the indication of SUI represents one of the most compelling emerging therapies" to date.[6] However, due to a lack of robust prospective data, the committee is unable recommend stem cell treatment outside of clinical trials. Thus, it is our responsibility as urologists and researchers to further investigate the use of stem cells in SUI in a rigorous, prospective, and comparative manner.

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Table 1.

Selected clinical studies of stem cell treatment for stress urinary incontinence

Study	Stem cell type	Study design	Outcomes	Conclusions
Carr et al., 2008	MDSCs	Sphincteric injections of autologous MDSCs in 8 women with SUI	After median follow up of 17 months, 5 out of 8 women showed improvement in sUI, with one achieving total continence.	Local stem cell therapy may be effective for SUI.
Carr et al., 2013	MDSCs	Sphincteric injections of autologous MDSCs in 38 women. Patients received either high (32–128 × 10^6 cells) or low dose (1–16 × 10^6 cells) treatment. Some women could elect to receive a second treatment after 3 months	After 12 months of follow up, 89% of women in the high dose group had ≥ 50% in reduction in pad weight compared to 62% in the low dose group. They also had a greater reduction in diary-reported stress leaks (78% vs. 53%). Side effects were minimal.	Local injection of MDSCs at a wide range of doses shows promise for relieving SUI and improving quality of life, with minimal side effects.
Stangel-Wojcikiewicz et al., 2013	MDSCs	Sphincteric injections of autologous MDSCs in 16 women with SUI. Dose of injected cells was 6 × 10^6	After 2 years of follow up, 50% of the patients were cured of SUI. A quarter of the patients were improved, and the remaining patients showed no improved symptoms. Side effects were minimal.	Local injection of MDSCs, even at a low dose, can provide durable relief of SUI symptoms in some patients.
Sébe et al., 2011	MDSCs	Sphincteric injections of autologous MDSCs in 12 women with SUI and fixed urethras after failed surgical management	After 12 months of follow up, 3 patients were dry according to a 7-day voiding diary and 1h pad test. In 7 other patients, pad test decreased while number of leaks/week did not. Quality of life was improved in half the patients.	Local injection of MDSCs in severe, multi-operated urethras can be a safe and effective therapy for SUI.
Blaganje et al, 2013	Myoblasts	Ultrasound-guided sphincteric injections of autologous myoblasts in 38 women. Patients also underwent post-operative transvaginal electrical stimulation for 5 weeks	Six weeks after treatment, 78.4% of patients had negative stress tests and reported subjective improvement in SUI. At 6-month follow-up, 52.6% reported improvement and 23.7% reported their incontinence cured.	Local injection of autologous myoblasts coupled with electrical stimulation may be a viable and safe treatment for SUI.
Kuismanen et al., 2014	ADSCs	Sphincteric injections of autologous ADSCs combined with bovine collagen in 5 women	After 1 year of follow up, 60% of patients had negative leak tests. All 5 patients reported subjective improvements	Local injection of ADSCs in combination with collagen may be safe and effective for the treatment of SUI in some patients

MDSC: muscle-derived stem cell, SUI: stress urinary incontinence, ADCS: adipose-derived stem cell

Table 2.

Selected pre-clinical studies of stem cell treatment for stress urinary incontinence

Study	Stem cell type	Study design	Outcomes	Conclusions
Carr et al., 2008	MDSCs	Sphincteric injections of autologous MDSCs in 8 women with SUI	After median follow up of 17 months, 5 out of 8 women showed improvement in SUI, with one achieving total continence.	Local stem cell therapy may be effective for SUI.
Carr et al., 2013	MDSCs	Sphincteric injections of autologous MDSCs in 38 women. Patients received either high (32–128 × 10^6 cells) or low dose (1–16 × 10^6 cells) treatment. Some women could elect to receive a second treatment after 3 months	After 12 months of follow up, 89% of women in the high dose group had ≥ 50% in reduction in pad weight compared to 62% in the low dose group. They also had a greater reduction in diary-reported stress leaks (78% vs. 53%). Side effects were minimal.	Local injection of MDSCs at a wide range of doses shows promise for relieving SUI and improving quality of life, with minimal side effects.
Stangel-Wojcikiewicz et al., 2013	MDSCs	Sphincteric injections of autologous MDSCs in 16 women with SUI. Dose of injected cells was 6 × 10^6	After 2 years of follow up, 50% of the patients were cured of SUI. A quarter of the patients were improved, and the remaining patients showed no improved symptoms. Side effects were minimal.	Local injection of MDSCs, even at a low dose, can provide durable relief of SUI symptoms in some patients.
Sébe et al., 2011	MDSCs	Sphincteric injections of autologous MDSCs in 12 women with SUI and fixed urethras after failed surgical management	After 12 months of follow up, 3 patients were dry according to a 7-day voiding diary and 1 h pad test. In 7 other patients, pad test decreased while number of leaks/week did not. Quality of life was improved in half the patients.	Local injection of MDSCs in severe, multi-operated urethras can be a safe and effective therapy for SUI.
Blaganje et al, 2013	Myoblasts	Ultrasound-guided sphincteric injections of autologous myoblasts in 38 women. Patients also underwent postoperative transvaginal electrical stimulation for 5 weeks	treatment, 78.4% of patients had negative stress tests and reported subjective improvement in SUI. At 6-month follow-up, 52.6% reported improvement and 23.7% reported their incontinence cured.	Local injection of autologous myoblasts coupled with electrical stimulation may be a viable and safe treatment for SUI.
Kuismanen et al., 2014	ADSCs	Sphincteric injections of autologous ADSCs combined with bovine collagen in 5 women	After 1 year of follow up, 60% of patients had negative leak tests. All 5 patients reported subjective improvements	Local injection of ADSCs in combination with collagen may be safe and effective for the treatment of SUI in some patients

MSC: mesenchymal stem cell, ADSC: adipose-derived stem cell, LPP: leak point pressure, MDSC: muscle-derived stem cell, AFSC: amniotic fluid-derived stem cell, SUI: stress urinary incontinence, ESC: embryonic stem cell, IPSC: induced pluripotent stem cell, pSMC: smooth muscle precursor cell, CCM: concentrated conditioned media