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Stem Cell Therapy for Incontinence: Where Are We Now? What is the Realistic Potential?

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Abstract

A significant number of women experience stress urinary incontinence (SUI), which greatly affects their quality of life. Recent research investigating utilization of stem cells and their derivatives for the prevention and treatment of SUI has been performed to test the effect of cell source and method of administration in several animal models of SUI. The type of stem cell, timing of optimal dose or doses after injury, mechanism of action of stem cells, and route of administration must be investigated both preclinically and clinically before stem cell therapy becomes a possible treatment for SUI, although the future of this therapy looks promising. This article reviews the progress in stem cell research for incontinence and describes areas of future work as suggested by research in other fields.

Keywords

Stem cell; Incontinence; Regenerative; Voiding dysfunction; Stress urinary incontinence; Women's health; Gynecology; Noninvasive therapy; Muscle-derived stem cells; MDSCs; Bone marrow-derived stem cells; BMSCs; Adipose-derived stem cells; ADCSCs; Human umbilical-cord blood cells; HUCBs

Introduction

Urinary incontinence and bladder dysfunction affect a large number of people, who experience a decreased quality of life due to social and sexual isolation as well as feelings of shame, anxiety, and depression [1]. As the elderly population increases, both the number of people who have a decreased quality of life due to these conditions and the economic burden of treating these dysfunctions are expected to increase dramatically [2].

Stress urinary incontinence (SUI) is typically treated with pelvic floor exercises, a bulking agent, or surgery. Duloxetine, a pharmaceutical agent, is approved for SUI treatment in some countries, but is not approved for this indication in the United States. Surgery remains the gold standard for bothersome cases and options include a Burch colposuspension procedure, an autologous fascial sling, and a midurethral synthetic sling. The latter has become the most common operation for SUI due to its minimally invasive nature, ease of use, and good long-term efficacy with up to 11 years of follow-up [3]. Nonetheless, up to a third of women undergo a second anti-SUI surgery due to recurrent SUI during their lifetime [4, 5]. In some patients, slings show no efficacy immediately after surgery and success rates decline steadily after surgery [6, 7].

There is a lack of noninvasive therapy successful at treating SUI over the long term, suggesting the potential for development of innovative procedures such as stem cell therapy. Various techniques using cells derived from various tissues (e.g., adipose and muscle tissues) utilizing different application techniques have been tested in several different animal models of incontinence [8]. Myoblasts have been tested for application to urology; however, in cardiology, myoblasts have been shown to have slower growth and poorer regeneration capabilities than stem cells [9]. Therefore, several studies have tested whether to use stem cells directly or to differentiate them into myoblasts or along other lineages before implantation [10–12].

Early clinical trials testing stem cells as a treatment for incontinence have used autologous muscle-derived stem cells (MDSCs) that have been injected directly either transurethral or periurethral [8]. A recent randomized blinded trial showed almost 50% improvement in patients 1 year after injection, although the study size was small [13].

Development of stem cell therapy for treatment of nonurological disorders, such as those in cardiology, is more advanced. Preclinical studies investigating safety, paracrine effects, source of cell, and efficacy have been completed [14–16, 17•, 18–24] and several randomized, double-blind, placebo-controlled clinical trials investigating both direct and intravenous infusion as well as dosage already have been done [25•, 26, 27]. An intracoronary infusion of autologous bone marrow or MDSC has been demonstrated to be safe in humans by the task force of the European Heart Association [28]. Because of the importance of delivery timing after injury due to the expression of cytokines and chemokines in the heart and blood, there currently are large, multicenter, randomized, double-blind, placebo-controlled clinical trials recruiting patients to evaluate optimal time points to deliver bone-marrow mesenchymal stem cells (BMSCs) after moderate to large myocardial infarction, particularly in high-risk patients [29, 30].

To reach this stage in the field of urology, or more specifically, incontinence, more basic science research comparing type of cells, dosages, timing of optimal dose or doses after injury, mechanism of action of stem cells, and route of administration must be performed. This will enable large multicenter clinical trials to focus on functional improvements, different treatments for stress, urge, or mixed incontinence, and potential adverse events. This article reviews the progress in stem cell research to treat or prevent incontinence and describes areas of future work as suggested by research in other fields.

Overview of Stem Cells

Stem cells are the current basis for tissue engineering and regenerative medicine. They are located in various parts of the body and replenish tissues, bone, and blood throughout life as well as enable healing after injury [31]. Stem cells are described by their differentiation potential: embryonic stem cells are totipotent, while adult stem cells are pluripotent or multipotent and cannot be differentiated into as many different types of tissues as embryonic cells [32]. Adult stem cells are, for the most part, tissue- or niche-specific, although the unique and defining markers for each stem cell population have not been found in vivo [31]. It is unknown whether adult stem cells are the same population of cells residing in different niches or separate populations with distinct characteristics and/or lineages [31]. These various questions arise because stem cells do not exhibit consistent signaling profiles or surface markers; rather, they act based on the cells and niche around them [31]. Because of this, various efforts to answer these questions have emerged. One study found mesenchymal stem cells with similar characteristics in many organs, including heart, kidney, spleen, and brain, and suggested that there is a common perivascular origin [33]. Other groups have compared stem cells isolated from adipose tissue, bone marrow, and umbilical cord blood and have found many similarities in morphology, phenotype, and gene expression [34, 35]. Further studies are needed to identify distinct characteristics and capabilities of each stem cell population, or if they are the same, how stem cells behave in different niches and what combination is the most effective.

Currently, a barrier to tissue engineering for clinical therapy is the lack of an adequate vascular supply for larger-volume implants [36]. Cells need to be within a tenth of a millimeter of a capillary to get the required oxygen for their processes as well as to remove waste products [37]. With the potential to create organs from stem cells, this problem can be overcome because it has been shown that stem cells induce neovascularization [9]. Although low cell retention and survival rate after transplantation are major problems with cell-based therapy, there is functional improvement despite the low number of engrafted cells in multiple injury models such as spinal cord injury, stroke, and myocardial infarction [22, 24, 38, 39].

Various mechanisms have been proposed to explain the reparative effects of stem cells because they are able to self-proliferate, differentiate, suppress immune function, release paracrine factors, and home to sites of injury [40]. Some researchers believe that direct engraftment and/or stem cell fusion or differentiation is responsible for improvement, while others believe trophic or paracrine factors influence the cells and microenvironment of the damaged tissue or organ. There is support for both arguments across fields, with some studies showing evidence of transdifferentiation or fusion in the target organ after direct injection to the injured area [41, 42] and others specifically showing that no fusion occurred [43]. Functional improvement also occurs when stem cells are injected into a distant uninjured muscle, indicating that factors released by stem cells distant to the injury may enable the reparative process [44••]. Injection of stem cell-produced factors or homing cytokines alone, without the actual stem cells, also has demonstrated functional improvement [16, 17, 45]. Specifically for incontinence, it has been shown that stem cell homing cytokines specific to mesenchymal stem cells, chemokine (C-C motif) ligand 7 (previously monocyte chemoattractant protein 3) and its receptor are upregulated in the urethra and vagina after a simulated childbirth injury in rats, suggesting that homing after injury is possible [46, 47]. In contrast, stromal cell-derived factor 1, the stem cell homing cytokine specific to hematopoietic stem cells, is not upregulated after this injury [46, 47].

It is currently uncertain whether stem cells should be injected as is or differentiated first into myoblasts, since myoblasts will only fill the defect as needed and then stop multiplying,

controlled presumably by cytokines and other factors [48]. However, it has been shown that stem cells generate larger grafts, have higher survival rates, and more effectively remodel injured cardiac tissue compared with myoblasts [9]. Overall, more is unknown than known in terms of optimal cell type, route of administration, mechanism of action, and the importance, or lack thereof, of engraftment and long-term survival.

Embryonic Stem Cells

Embryonic stem cells are totipotent and have the capability to differentiate into the three embryonic germ cell layers (endoderm, mesoderm, and ectoderm), making them attractive for use in regenerative medicine [40]. Although embryonic stem cells have not been used for incontinence, they have been utilized to investigate the possible creation of renal tubules or generation of functional bioartificial renal units for patients with renal failure [49, 50]. They also were used to create sperm in previously infertile male mice, although there has not yet been successful gamete creation [51, 52]. However, there are serious concerns about tumorigenicity [53]. Furthermore, the political and ethical debates concerning obtaining and using embryonic stem cells limit their current potential therapeutic use [54].

Bone Marrow–Derived Mesenchymal Stem Cells

Bone marrow contains heterogeneous populations of cells, including erythrocytes, macrophages, endothelial cells, fibroblasts, and adipocytes, as well as hematopoietic and mesenchymal stem cells [40]. BMSCs currently are the principally used cells both preclinically and clinically [40]; however, they are less commonly utilized in urology or incontinence research [8]. This may be due to the fact that although BMSCs are pluripotent cells characterized as capable of differentiating easily into osteogenic, adipogenic, and chondrogenic lineages [55, 56], the procedure for bone marrow removal/aspiration is painful, requiring general or spinal anesthesia, and may be more tolerable for cardiac injury as opposed to the treatment of incontinence [57, 58].

BMSCs injected in two sites periurethrally 2 weeks after a bilateral pudendal nerve transection were found to improve function as assessed by measurement of leak point pressure (LPP) and urethral closure pressure 1 month after injection [59•]. The injected cells stained positive for smooth muscle actin, vimentin, and desmin and formed dorsolateral muscle masses at the injection sites, effectively compressing the urethral lumen and acting as a bulking agent [59•]. Similar results have been observed in experiments in vitro when BMSCs stained positive for desmin and smooth muscle actin and expressed myosin heavy chain [11, 60], indicating differentiation of BMSCs into smooth and striated muscle under appropriate conditions. When BMSCs were implanted periurethrally into atrophic urethras (damaged by pudendal nerve transection), the sites of injection and newly formed tissue stained positive for desmin and myosin heavy chain, indicating the presence of striated skeletal muscle as confirmed by histological analysis and improved LPP [60].

These results differ somewhat from that of Kinebuchi et al. [61•], who found no difference in LPP with a urethrolisis injury between control and BMSCs, but did note that BMSCs differentiated into striated muscle and peripheral nerve cells but not smooth muscle. It is possible these differences exist because of the differences in injury models, time point of injection after injury, and functional test time point after injury.

In one interesting study, BMSCs were combined with a sling model in rats after bilateral sciatic nerve transection [62•]. While both a sling with and without BMSCs demonstrated good functional outcomes using LPP, the BMSC-seeded sling had a better ligament-like formation after 12 weeks, higher force to failure, and more collagen matrix deposition [62•]. A combination stem cell sling possibly is a promising integration method that may provide

long-term success for both structural and functional support of the deficient urethral sphincter in humans.

Muscle-Derived Stem Cells

Muscle tissue represents a valuable and easily accessible source of adult stem cells. Their procurement entails minimal morbidity and can be done under local anesthesia [63]. Though in the past there were technical difficulties associated with growing these cells and selecting for stem cells, this technical difficulty seems to have been overcome by various preplating techniques [64–66]. In short, to obtain MDSCs, muscle tissue is enzymatically digested, then cultured for a short period of time to allow fibroblasts to attach to the plate or flask. The supernatant that now contains the myogenic fraction, and therefore, the MDSC precursor, is then transferred to a new flask, thereby enriching for the desired cells which are collected several days after seeding [66]. Several studies have shown that MDSCs are capable of proliferation, multipotent differentiation, and self-renewal [66, 67], indicating their potential for tissue regeneration.

When compared with saline treatment after transection of the sciatic nerve in rats, both fibroblasts and MDSCs injected intraurethrally increased LPP, but muscle of MDSC-injected urethras contracted with 27% greater amplitude, while the fibroblast-injected urethras eventually became obstructed [68]. Furuta et al. [58] also investigated LPP and contractile responses of the proximal urethra 6 weeks after an injection of human MDSCs into the proximal urethras of female nude rats that had previously received bilateral pudendal nerve transection [58]. There was no significant difference between the LPP in sham-operated saline-treated rats and nerve transected rats injected with MDSCs, indicating a return to normal in the stem cell-treated animals. However, after application of hexamethonium, which blocks autonomic efferent nerves, the LPP in nerve-transected rats with MDSCs was significantly decreased compared with the sham-operated saline-treated group. The contractile responses to phenylephrine, but not to carbachol, in nerve-transected rats with MDSCs were significantly increased compared with sham-operated, saline-treated and nerve-transected, saline-treated groups [58]. These results suggest that the functional improvements mediated by MDSCs are due to improvements in smooth muscle innervated by autonomic nerves [58].

In a pudendal nerve denervation model in rats, Lee et al. [69] showed that a periurethral injection of MDSCs increases LPP and urethral closure pressure 4 and 12 weeks after injury, and was superior to bovine collagen 12 weeks after injury. There was no immunogenic reaction or severe lymphocyte reactions observed at the site of injection [69]. The investigators observed an increase in skeletal muscle mass at the sites of injection, suggesting conditions different from that of the experiments of Furuta et al. [58], who demonstrated that functional improvements were due to changes in smooth muscle.

When MDSCs were mixed with fibrin glue and injected into the urethra after pudendal nerve transection in rats, the number of surviving MDSCs was significantly increased [70]. There was an increased muscle-to-collagen ratio and microvessel density, demonstrating that fibrin glue may potentially promote cell attachment and proliferation [70]. Chancellor et al. [71] demonstrated that MDSCs are capable of proliferation to form myoblasts in vivo, which then will fuse, when mature, in postmitotic (i.e., no longer dividing) myotubes, limiting growth and avoiding the risk of a potential obstruction of the urinary tract [71]. Kajbafzadeh et al. [72] injected autologous myoblasts transurethrally followed by postoperative pelvic floor electrical stimulation, which demonstrated an improvement of urinary incontinence in children with bladder exstrophy, indicating the potential to combine the myoblasts or MDSCs with traditional treatment.

All clinical trials on incontinence have used autologous MDSCs and injected them directly into the urethra either transurethrally or periurethrally. The first was done by Strasser et al. [73] with improvements in quality of life and thickness and contractility of the urethral sphincter, with a success rate of over 90% for women and over 50% for men [73]. However, this study was later retracted due to breaches in ethical guidelines and protocol irregularities [74]. In North America, a small clinical trial with eight women showed more modest and realistic improvements and changes, with one patient achieving complete continence and four indicating improvement from baseline 1 year after the initial injection [75]. A larger, blinded, and randomized trial by the same group had an almost 50% cure rate in patients 1 year after two injections and other slightly different techniques as evidenced by the increased dry percentage [13].

Preliminary clinical data from a multicenter study demonstrated that intrasphincteric injection of autologous MDSCs at various doses reduced the amount of leakage during a 24-hour pad test and lowered the incidence of diary-reported stress leaks over 3 days. These improvements started as early as 1 month after injection and lasted through the study's end point of 6 months, with some evidence suggesting that the higher doses of MDSCs are associated with greater and faster improvement of incontinence symptoms, although not all patients improved (even at the highest dose or the longest time point) and no cure or "dry" rates were reported [76]. All minor complications associated with treatment occurred at low rates and either resolved independently or were easily treated, suggesting the feasibility of utilizing MDSCs as a therapy for SUI. Because most preclinical studies are done in acute injury models, this is an important result demonstrating stem cell efficacy long after the injury has occurred. Although the authors did not speculate on the mechanism of action of the cells, it is interesting to note that the effect of treatment occurred as late as 1 to 6 months after the actual injection.

Adipose-Derived Stem Cells

Adipose-derived stem cells (ADSCs) are plentiful and can be obtained by minimally invasive lipoaspiration of the abundant adipose tissue in humans [77]. Several studies have shown that ADSCs are multipotent cells and are capable of differentiating into adipogenic, chondrogenic, myogenic, and osteogenic cells [57, 77]. Rodriguez et al. [78] showed that ADSCs can be obtained from processed lipoaspirate and are able to differentiate into functional smooth muscle cells capable of contraction with cholinergic stimulation, followed by relaxation similar to normal muscle tissue.

In a rat postpartum vaginal balloon dilation and bilateral ovariectomy model of simulated childbirth, ADSCs were derived from periovarian fat and then reinjected either via the tail vein or directly into the urethra [79••]. Both injection routes resulted in a higher concentration of elastin and smooth muscle in the urethra as well as an improvement in voiding function 4 weeks after injection. ADSCs were detected in the connective tissue along and underneath the urothelium [79••].

ADSCs combined with nerve growth factor (NGF) encapsulated within poly(lactic-co-glycolic acid), or PLGA, microspheres were injected directly into the urethra by Zhao et al. [80•]. NGF-PLGA microspheres increased cell survival and retention in the urethra, and 8 weeks after treatment, rats with ADSCs and NGF-PLGA microspheres were recovered significantly more than all the other groups (saline-treated [phosphate-buffered saline], ADSC and NGF only, ADSC and PLGA only, and ADSC-only treated groups). Both LPP and retrograde urethral perfusion pressure, returned to levels comparative to that of an uninjured rat [80•].

ADSCs also have undergone induction into myoblasts and appear to be typical smooth cells expressing sarcomeric and desmin proteins both in vitro [12] and in vivo after direct injection into the urethra [10]. Fu et al. [10] used an injury model combining ovariectomy followed by a weighted vaginal distention intended to model a difficult childbirth and menopause. Myoblasts (induced from ADSCs) or ADSCs (as a control) were injected 3 months after the injury, and there was no difference between injections 1 month after injection; however, at 3 months after treatment, the rats that received a myoblast injection had fully restored LPP and functional bladder capacity [10]. Animals with a myoblast injection had thicker smooth muscle and more longitudinal muscle fibers explaining the increased function as compared with ADSC-treated rats. This is an interesting result that conflicts with other researchers who found myoblasts did not have a positive effect on left ventricular function after infarction in a blinded randomized trial [81] and that myoblasts are inferior when compared to MDSCs in grafting and surviving oxidative stress, among other cases [9]. Furthermore, other researchers have had success with ADSCs, although Zhao et al. [80•] found that ADSCs alone did not demonstrate as much recovery as ADSCs mixed with NGF-PLGA microspheres. Perhaps the differences are due to differences in processing and isolation, because in the study by Fu et al. [10], neither the ADSCs nor myoblasts were selected for cell surface markers, so the populations are potentially heterogeneous and mixed.

In a clinical study, ADSCs harvested and purified from lipoaspiration were injected periurethrally in two male patients after radical prostatectomy [82]. Urinary incontinence progressively improved after 2 weeks of injection and persisted up to 12 weeks after treatment, with decreases in leakage volume and increases in quality of life, maximal urethral closure pressure, and functional urethral length. A bulking effect was demonstrated on magnetic resonance imaging 12 weeks after treatment, indicating that ADSCs may have contributed to the improvement of sphincteric function [82]. Interestingly, there was a sequential increase in blood flow to the region after ADSC injection that persisted for at least 12 weeks, potentially indicating the effect of cytokines secreted from stem cells causing neovascularization [83]. Unfortunately, this work was later retracted due to a breach of ethical research guidelines, and therefore, needs to be repeated and validated under appropriate ethical research approval [84].

Human Umbilical Cord Blood Stem Cell

Human umbilical-cord blood cells (HUCBs) are derived from the trophoblast and are not considered embryonic cells. Therefore, these cells potentially have an advantage over progenitor cells from other sources because of their young chronologic age [85]. Because stem cells from older patients divide fewer times and have less differentiation potential than stem cells from young patients [86], HUCBs may represent a useful source of cells for transplantation to restore sphincter function. In addition, using stem cells obtained from cord blood avoids invasive procedures [87].

Preclinically, Lim et al. [88] demonstrated that rats that received HUCB after electrocauterization of periurethral tissue had significantly improved LPP, and that histologically, the urethral sphincter of rats that received HUCBs was identical to that of an uninjured rat. In this study, most HUCBs were found in the lamina propria beneath the urethral mucosa, with a few cells found between the muscle layers of the urethral sphincter. Although the authors suggest that the functional improvement was not due to changes in the sphincter [88], paracrine effects from this nearby area are still possible, especially because after the injury and HUCB treatment, the sphincter was not disrupted as it was in the untreated animals.

HUCBs also have been tested in female patients with incontinence stemming from intrinsic sphincter deficiency, mixed incontinence, or urethral hypermobility [89]. At 12 months after treatment, 72% of patients had more than 50% improvement of their incontinence symptoms [89].

Other Sources

Potentially, there are stem cells sources for treatment of incontinence and urological reconstruction that involve less-invasive procedures than those described above. Hair follicle cells have been found to contain adult stem cells that are multipotent and differentiate into adipogenic, osteogenic, and epithelial lineages depending on isolation and culture procedures [90, 91]. Additionally, they were found to contain p63, a protein necessary for formation of urothelium [92]. An even less-invasive method for collecting cells would be from urine: two to seven multipotent stem cells have been isolated per 100 mL of urine, along with many other stem/progenitor cells that did not expand in culture, and cells that were partially or fully differentiated that washed off with the first media change [93]. Urine progenitor cells (about 0.2% of the cellular population in urine) stained positive for CD73, CD90 (Thy-1), and CD105 (endoglin), markers that are characteristic of mesenchymal cells, and stained negative for CD45, CD31, CD34, and other hematopoietic and endothelial lineage markers [93].

Conclusions

Although there has been a fair amount of preclinical research on utilization of stem cells and their derivatives as treatments for incontinence, much research still needs to be done before these therapies can be introduced into practice. Larger multicenter clinical trials that are double-blinded and placebo-controlled must be done; however, there is still much preclinical investigation to be done before we reach that point.

It is unknown which cell type or injection site is more effective in treatment, or if different cell types may be superior for different types of incontinence. All of these can be elucidated once various cell types and methods of administration are tested in the same animal injury model. Additionally, different stem cells may respond to injury in different ways, and stem cells used to treat incontinence may have a unique response due to the compound neuromuscular injury of childbirth. Thus, it may be difficult to extrapolate information from other fields into the field of incontinence. Therefore, the optimal cell type cannot be determined until these preclinical investigations occur.

It also is not known if the primary action of stem cells is by differentiation into smooth or striated muscle, by paracrine action of trophic factors produced by injected stem cells on innate tissues, by a combination of paracrine effects and immunosuppression, or by another mechanism as yet undelineated. It is important to note that the mechanism of action for stem cells is still not fully determined in any field, but there is some evidence for paracrine effects, as well as transdifferentiation [41–45].

Once the mechanistic action of each type of stem cell with therapeutic potential is determined, this information then can be used to determine what combination of stem cell source and method of administration is likely to be most effective in treating or preventing incontinence of various types. In addition, it ought to drive choices regarding the appropriate dose of cells and number of treatments. If retention of stem cells in the target organ is shown to be important for enhancing the mechanism of action of stem cells, substances that enhance cell retention and survival should be further investigated.

Aside from injecting cells for treatment of incontinence, stem cells may be combined with existing treatment options, such as slings, as evidenced by Zhou et al. [62•]. This potentially could improve the long-term efficacy of slings and reduce complications such as erosion or extrusion of synthetic slings, although this needs to be studied further both in preclinical animal models and in clinical trials.

In summary, although much work needs to be done both preclinically and clinically before stem cell therapy can replace surgery as the mainstay of treatment of stress urinary incontinence, the future looks promising.

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