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Review Article

Stem-cell therapy in stress urinary incontinence: A review

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Abstract

The incidence of urinary incontinence (UI) is approximately 10%–40% in women, affecting one to two hundred million women worldwide. Stress UI (SUI) is characterized by involuntary urination due to increased abdominal stress and urine leakage without bladder contraction. Surgical treatments include midurethral slings, bulking agents, and Burch colposuspension to restore urethral continence. Nevertheless, an optimal treatment for all types of incontinence has not yet been established. Stem-cell therapy has emerged as a novel treatment for many diseases. Stem cells can self-renew and can differentiate into other cell types. Adult stem cells are suitable for clinical applications because they can be easily obtained noninvasively or minimal invasively. Stem-cell therapy for SUI has been studied preclinically and clinically. Muscle-derived progenitors have been used to treat SUI by promoting the regeneration of rhabdomyosphincters. The human trial used transurethral injection of autologous muscle-derived stem cells to improve sphincter contractility and function. Other sources of stem cells have also been studied in SUI treatment, such as umbilical cord blood, amniotic fluid, bone marrow, urine, and adipose tissue. The success rate of stem-cell therapy for SUI ranges from 13% to 100%. This review aimed to summarize the current status of stem-cell treatments for SUI, with respect to clinical trials, cell types, transplantation routes, and dosage volume and frequency.

Keywords: *Mesenchymal stem cell, Myofibroblast, Stem cells, Stress urinary incontinence, Treatment*

Introduction

The incidence of urinary incontinence (UI) is approximately 10%–40% in women, affecting one to two hundred million women worldwide [1]. Stress UI (SUI) is characterized by involuntary urination due to increased abdominal stress and urine leakage without bladder contraction [2]. In women, the peak age of incidence is 45–49 years of age. SUI causes hygiene and social problems [3].

SUI can arise from anatomic incontinence, also known as hypermobile urethra and intrinsic sphincter deficiency (ISD). Surgical treatments for anatomical incontinence include bladder neck suspension [4] and insertion of a midurethral sling [5]. Surgical treatment for ISD involves sling implantation and urethral submucosal injection of blocking agents (fat tissue, Teflon, collagen, or silicone) [6]. Nevertheless, an optimal treatment for all types of incontinence has not been established.

Stem cells have emerged as a novel treatment for many diseases [7,8]. Stem cells can self-renew and differentiate into other cell types. Adult stem cells are better suited for clinical applications because they can be easily obtained without an invasive procedure, unlike embryonic stem cells (ESCs) [7]. Stem-cell therapy for SUI has been studied both preclinically and clinically. Muscle-derived progenitor cells have been used to treat SUI by promoting the regeneration of rhabdomyosphincters [9,10]. Strasser *et al*. reported the first human trials to perform transurethral injection of autologous muscle-derived stem cells (MDSCs) [11]. A thickened urethral sphincter and improved sphincter contractility were noted after stem-cell transplantation. Other sources of stem cells have also been studied, such as umbilical cord blood, amniotic fluid, bone marrow, urine, and adipose tissue [12].

This study aimed to review the current status of stem-cell treatments for SUI, with respect to clinical trials, cell types, transplantation routes, and dosage volume and frequency.

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Stress urinary incontinence

SUI is the involuntary leakage of urine during physical exertion [13]. The prevalence in the female population ranges from 25% to 45% and increases with age [13]. Pregnancy, vaginal delivery, obesity, constipation, and smoking are risk factors for SUI [14]. SUI significantly influences the quality of life and socioeconomic status of female patients. SUI can result from urethral hypermobility and ISD [15]. The urethral continence control system, which consists of striated muscle, smooth muscle, connective tissue, the submucosal vascular plexus, and the epithelial lining, plays an important role in SUI [15]. Striated muscle has been shown to be largely responsible for maintaining intraurethral pressure [16]. Damage to striated muscle can result from birth or surgical injuries. Advanced age also leads to spontaneous apoptosis and loss of striated muscle cells of the rhabdosphincter [14].

Current therapies for stress urinary incontinence

Conservative therapy includes behavioral therapy, biofeedback, insertion of vaginal pessary, and pelvic floor muscle training [17,18]. More invasive procedures may be recommended to restore urethral continence if conservative treatments fail and can involve implantation of a midurethral mesh sling [5], injection of bulking agents [6], and Burch colposuspension [4]. These procedures achieve approximately 80% continence 1 year after surgery, but the continence rate has been shown to decrease over time [19]. However, mesh slings are associated with a risk of exposure or erosion [19]. Periurethral and transurethral injection of bulking agents is a standard technique for the treatment of UI and is less invasive than surgical procedures [6]. However, the overall success rates of current therapies are unsatisfactory and offer only short-term relief [6].

Stem cells

Stem cells can self-renew and differentiate into different cell types [7]. The two major types of stem cells are pluripotent stem cells (PSCs) and mesenchymal stem cells (MSCs). PSCs include ESCs and induced iPSCs. ESCs are obtained from the inner cell mass of blastocysts and are capable of tumorigenesis. The use of ESCs for clinical treatments has ethical and legal considerations [7]. Thus, iPSCs have been developed to address the ethical concerns of ESCs. iPSCs are generated via the transduction of four genes – Nanog, c-Myc, Klf4, and Sox2 – into fibroblasts [20]. iPSCs are currently undergoing clinical trials in Japan to treat retinopathy [21]. MSCs are stromal cells that undergo trilinear differentiation [22]. MSCs can be isolated from a variety of tissues, including bone marrow, umbilical cord, endometrial, and adipose tissue [7]. In addition to their regenerative ability, MSCs also have anti-inflammatory and immunomodulatory characteristics. MSCs can be harvested autologously, and the number of clinical trials evaluating their utility and safety for medical purposes is high (>950 clinical trials) [22,23]. The clinical applications of MSCs can be broadened by understanding intracellular and intercellular signal transduction, dosage adjustment, tissue engineering, and patient selection [22].

Benefits and drawbacks of stem-cell treatment for stress urinary incontinence

The current therapy for SUI is implantation of a mesh sling, which has a long-term durable response [24]. However, sling operations may result in complications such as urinary retention, wound issues, mesh erosion, and wound pain [25]. Intraurethral or periurethral injectable therapies have become minimally invasive. The benefit of this intervention is that there is no visible scar; however, the outcomes may not be durable or the therapy may not be efficacious. In addition to bulking agents, stem cells can be injected as a form of regenerative therapy. Previous preclinical and clinical studies using this therapy have shown promising results with low morbidity, and the injection process is associated with less morbidity than the sling operation [26]. However, stem-cell therapy for SUI may be hindered by economic costs. In Taiwan, the use of autologous adipose-derived stem cells (ASCs) for treatment costs 7000 US dollars. Without insurance coverage, most patients cannot afford such high costs. In conclusion, stem-cell therapy for SUI is promising and effective, but its cost is prohibitively high.

The effect of stem cells on the urethral sphincter in animal models

Several methods have been used in animal models to test the effectiveness of stem-cell therapies at improving sphincter function. The first method involves midurethral cauterization to cause urethral injury followed by transplantation with MDSCs [27]. After injection for 1 week, the leak point pressure (LPP) increased and improved at 2, 4, and 6 weeks after injection [27]. Immunohistochemistry of treated tissues demonstrated that stem cells can integrate into the striated muscle layer of the rat urethra. The second method involves pudendal nerve dissection to cause urethral dysfunction 2 weeks before stem-cell treatment [28]. After injection of bone marrow MSCs, LPP and urethral closure pressure were restored 4 weeks after treatment. The injected bone marrow MSCs tested positive for muscle-specific markers. The third method involves causing SUI via vaginal distension [29]. After ASC injection, maximal bladder capacity and LPP increased significantly at 1 and 3 months postinjection. Immunohistochemistry showed thickening of the inferior muscularis in urethral mucosa, which may contribute to sphincter function improvement. Other methods include urethrolysis, pubourethral ligament dissection, urethral sphincterectomy in old multiparous female animals, transgenic animals, and knockout animals [30]. Muscle precursor cells were injected, and functional sphincter recovery was noted after transplantation in a large animal model (nonhuman primate model) [31]. In conclusion, stem-cell transplantation can be used to recover sphincter and urethral function.

Types of stem cells used to treat stress urinary incontinence

Mesenchymal stem cells

MSCs have demonstrated safety and efficacy against UI in experimental models [32]. Various clinical trials have examined

the safety of different MSCs for the treatment of UI, including MDSCs, ASCs, bone-marrow-derived mesenchymal stem cells (BMSCs), urine-derived mesenchymal stem cells (UDSCs), amniotic fluid stem cells (AFSCs), and umbilical cord blood stem cells (UCBSCs) [32] [Figure 1]. Many differences exist among these different MSCs, including cellular origin, application system, success rate, and follow-up [12,33].

Muscle-derived stem cells

MDSCs have been extensively studied as a method of SUI treatment [12]. Cultivation of MDSCs may result in minimal morbidity when muscle biopsies are performed under local anesthesia [34]. The retrieved muscle tissue needs to be expanded *in vitro* and reinjected into the paraurethral region [35]. MDSCs have been shown to have great potential for regeneration [36]. MDSCs can be injected transurethrally or periurethrally into the rhabdosphincter to improve sphincter function and can be used as blocking agents [12,35].

Adipose-derived stem cells

ASCs can differentiate into various types of cells, including myoblasts, fibroblasts, endothelial cells, smooth muscle cells, and neurogenic cells [37,38]. ASCs are being increasingly used, owing to their abundance and availability. Furthermore, periurethral injection of ASCs induces *in vivo* differentiation into smooth muscle cells [38]. Only four papers have been published on ASCs for the treatment of UI. One study treated 11 male patients with stromal vascular fraction cells [39]. Another study was a pilot study that treated five female patients with ASC cultures combined with bovine collagen [40]. Finally, ASCs were used to treat patients in two phase I clinical trials, one of which included six male SUI patients who had had a radical prostatectomy [41], while the other included 10 female SUI patients [41].

Bone marrow mesenchymal stem cells

BMSCs were the first stem cells to be discovered [7]. BMSCs are found in the bone marrow and are frequently used in cell replacement therapy. A drawback to the use of BMSCs is that the process of obtaining bone marrow is painful under local anesthesia, thereby requiring the use of general anesthesia. BMSCs can expand *in vitro* for a short period and can be injected. Nevertheless, BMSCs have not been used to treat SUI. Gunetti *et al*. demonstrated that BMSCs can be used for the treatment of UI *in vitro* and *in vivo* in animal models, with high success [42].

Urine-derived mesenchymal stem cells

UDSCs can be easily recovered from urine and cultured *in vitro*. The collection of UDSCs is easy, noninvasive, and low cost. Nevertheless, few studies on UDSCs for the treatment of UI have been conducted. Zhang *et al*. collected 55 urine samples from 23 individuals [43]. They found that collected UDSCs can expand *in vitro* and can differentiate into cells that express urothelium, smooth muscle, endothelial, or interstitial cell markers.

Amniotic fluid stem cells

AFSCs are multipotent ESCs that are derived from amniotic fluid [44]. They can be obtained noninvasively via routine amniocentesis and expanded *in vitro*. The cells' phenotype and genotype have been shown to be stable during culture. AFSCs have been reported to have therapeutic effects in animal models of bladder dysfunction [44,45]. Chun *et al*. used a nephrectomized mouse model and transplanted human AFSCs into the urethral sphincter [46]. The urodynamic study showed an improvement in LPP in the triple-cell combination group (muscle/neuron/endothelial cells). This improvement

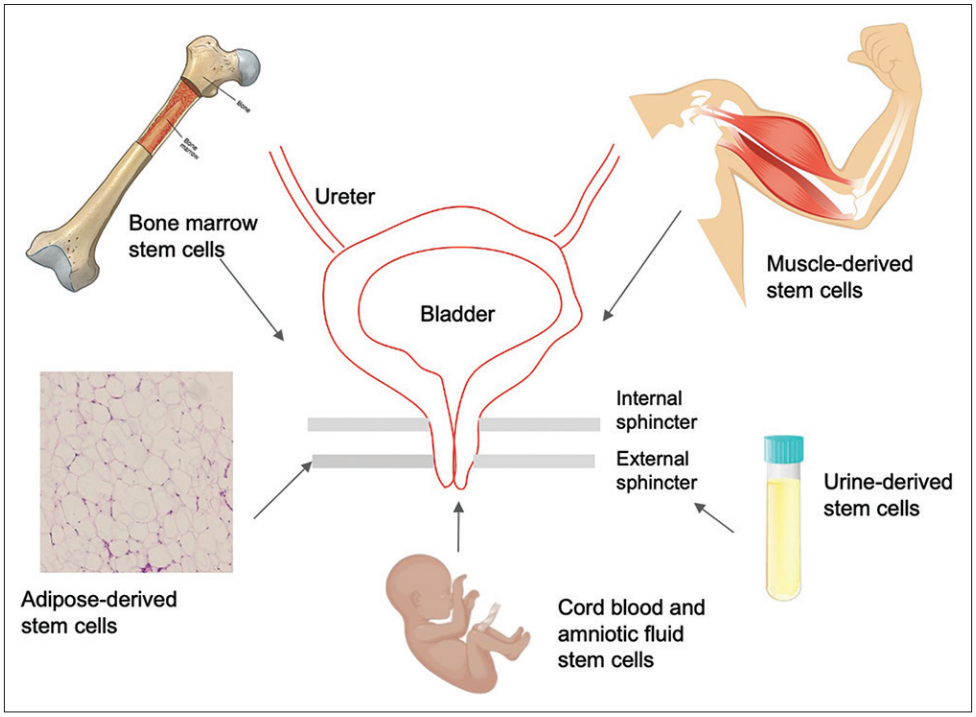

Figure 1: The different tissue-derived stem cells used to treat stress urinary incontinence

was confirmed via histological and molecular analyses. However, we are not aware of the use of AFSCs in any clinical trials for SUI treatment.

Umbilical cord blood stem cells

UCBSCs can be harvested from human umbilical cord blood [8]. UCBCSs are considered to be of fetal origin and have better differentiation capabilities than adult stem cells [8]. Another advantage is that the collection process is as easy, as the collection of UDSCs does not involve any invasive procedures. UCBSCs are also under investigation and have shown promising results in many animal models of degenerative diseases, such as cerebral ischemia and spinal cord injuries [47,48]. UCBSCs also have a low risk of graft-versus-host diseases and viral contamination. HLA type matching can be less stringent. Moreover, UCBSCs can be obtained from donor-based banking systems [49]. In summary, the use of UCBSCs can be as a form of SUI treatment.

Table 1: Clinical trials using muscle-derived stem cells to treat stress urinary incontinence

Publication year/Author	Patients (*n*)	Cell dose (cells)	Route of injection	Number and sites of injection	Follow-up (months)	Success rate (%)
2007/Mitterberger *et al*. [50]	123 females	2.8×10^7	Transurethral (TUUS-guided injection)	15-18 Mid-portion of the urethra; omega-shaped rhabdosphincter at 2 different levels	12	94/119 (79)
2008/Mitterberger *et al*. [56]	63 males	2.8×10^7	Transurethral (TUUS-guided injection)	15-18 Mid-portion of the urethra; omega-shaped rhabdosphincter at 2 different levels	12	41/63 (65)
2008/Mitterberger *et al*. [57]	20 females	$1.0-3.0\times10^7$	Transurethral (TUUS-guided injection)	15-18 Mid-portion of the urethra; omega-shaped rhabdosphincter at 2 different levels	24	18/20 (90)
2008/Carr *et al*. [58]	8 females	$18-22\times10^6$	Periurethral and transurethral (cystoscope guided)	2-4 3, 6, 9, and 12 o'clock positions	12	5/8 (62.5)
2011/Sèbe *et al*. [51]	12 females	G1: 1×10^7 G2: 2.5×10^7 G3: 5×10^7	Transurethral (endoscope guided)	2 3 and 9 o'clock positions	12	3/12 (25)
2012/Blaganje and Lukanović [52]	38 females	$1\times10^6-5\times10^7$	Transurethral	26 Transurethrally under direct visualization at 2 different levels of the rhabdosphincter	1.5	5/38 (13)
2013/Carr *et al*. [53]	38 females	Low doses: 1, 2, 4, 8 or 16×10^6; High doses: 32, 64 or 128×10^6	Periurethral	2 2 areas of the external urethral sphincter	12	29/38 (76)
2014/Gräs *et al*. [54]	35 females	NA	Periurethral	2 9, 12, and 3 o´clock positions, at a distance of 0.5-1 cm from the orifice	12	5/20 (25)
2014/Peters *et al*. [55]	80 females	10, 50, 100 or 200×10^6	Transurethral	8 Mid-urethra	12	40/80 (50)
2014/ Stangel-Wojcikiewicz *et al*. [59]	16 females	$0.6-25\times10^6$	Transurethral (endoscope guided)	3 9, 12, and 3 o'clock positions	24	8/16 (50)
2016/Sharifiaghdas *et al*. [60]	10 females	38.6×10^6	Transurethral (endoscope guided)	4 2, 5, 7, and 11 o'clock positions	36	3/10 (30)
2018/Jankowski *et al*. [61]	93 females	150×10^6	Transurethral	9 3, 6, and 9 o'clock positions	24	52/91 (57.1)
2022/Blaganje and Lukanović [62]	38 females	0.2×10^6	Transurethral (ultrasound guided)	26 Extrinsic urethral sphincter in 2 different levels of the sphincter	24	25/31 (80.6) CGI-S score

TUUS: Transurethral ultrasound, MDSC: Muscle-derived stem cells, CGI-S score: Clinical Global Impression - Severity Score

Clinical trials regarding stress urinary incontinence treatment

In human trials of stem cells for the treatment of UI, cell sources include MDSCs [50-55], ASCs [40], and UCBSCs [49]. Many differences exist between stem-cell studies in terms of cell origin, mode of operation, success rate, and length of follow-up [12,33].

Muscle-derived stem cells

Thirteen clinical trials studying the use of MDSCs in SUI treatment have been conducted [Table 1]. Carr *et al*. recruited eight women treated with autologous MDSCs and followed up with them after 1 year [58]. They found that 62.5% (5/8) of the patients experienced symptom improvement, and one patient had complete continence. Another study by Carr *et al*. recruited 38 female patients treated with a low (n = 20) or high dose (n = 12) of MDSCs. All patients experienced a significant reduction in the number of wet pads, with better results observed in the group that was administered the higher dose. Mitterberger *et al*. recruited 123 female patients (follow-up after 62.9 months) who showed a significant improvement in SUI after myoblast and fibroblast injection [50]. At the 1-year follow-up, 79% (n = 94) of the patients were continent with 13% (n = 16) experienced significant improvement.

Stangel-Wojcikiewicz *et al.* recruited 16 female patients and recorded improvement in 25% of patients, with respect to clinical and urodynamic parameters (Valsalva LPP and cough leak detection pressure) [59]. Sharifiaghdas *et al*. conducted a prospective cohort study of 10 female patients receiving MDSCs for SUI treatment [60]. After a follow-up period of 3 years, three patients recovered full continence, as measured by a cough stress test, a 1-h pad test, and a questionnaire. Four patients showed a significant improvement, and three patients did not respond to the treatment.

Gerullis *et al.* recruited 222 patients who had undergone a urological procedure (192 radical prostatectomies, nine transurethral resections of the prostate, and 21 radical cystoprostatectomies accompanied by neobladder construction) and who were treated with autologous MDSCs [63]. After a follow-up of 6–12 months, 12% (n = 26) of patients were continent, 42% (n = 94) showed improvement, and 46% (n = 102) had persistent UI. Mitterberger *et al.* conducted a study of 63 male patients with UI after a radical prostatectomy treated with MDSCs and reported that 65% (n = 41) of patients had complete continence and 27% (n = 17) of patients had improved significantly at the 1-year follow-up [56]. Another study by Mitterberger *et al.* recruited 123 female SUI patients treated with MDSC injections [50]. At the 1-year follow-up, 94 women (79%) were completely continent, and 16 (13%) and nine (8%) showed substantial and slight improvements, respectively. Mitterberger *et al.* also recruited 20 female patients with SUI and treated them with 1–3 × 10^7 MDSCs [57]. At the 1-year follow-up, 18 patients were cured, and SUI improved in the other two patients. The treatment effect was maintained at the 2-year follow-up. Quality of life scores significantly improved after transplantation.

Blaganje and Lukanović recruited 38 patients with SUI with transplanted MDSCs [62]. After follow-up at 2 years, the improvement in SUI was evaluated using the incontinence episode frequency score, short pad test, quality of life, and patient and clinician perceptions, and all showed a significant improvement. They concluded that MDSC injection is feasible and safe in patients with SUI and that the quality of life significantly improved. Sèbe *et al.* recruited 12 female patients with SUI and treated them with MDSCs [51]. Three of the 12 patients (25%) were dry on the pad test at 12 months, and 7 (58.3%) of the other patients showed improvement. Quality of life improved in six of the 12 (50%) patients.

Overall, MDSC treatment for SUI is feasible and effective [Table 1]. The success rates ranged from 13% to 90%. However, the follow-up period was short. Further large-scale trials are required to confirm its efficacy.

Adipose-derived stem cells

ASCs are currently the most commonly used type of stem cell in plastic transplantation. A large amount of adipose tissue can be obtained through liposuction, and repeated sampling is possible. ASCs undergo a wide range of differentiation processes, including adipogenesis, osteogenesis, chondrogenesis, and myogenesis [64].

Yamamoto *et al.* recruited three male patients with SUI and treated them with ASCs [65]. At the 6-month follow-up, decreased leakage volume, decreased frequency and amount of incontinence, and improved quality of life were recorded. Both the functional profile length and maximum urethral closing pressure increased. They concluded that ASC treatment for male SUI is safe and feasible.

In 2014, Kuismanen *et al*. reported a prospective generational study of ASCs injected into the human urethra in which five female patients with SUI received autologous ASC injections [40]. After 1 year of follow-up, all patients had a negative cough test. The overall UI scores significantly improved [40]. This study also showed that the use of stem cells for the treatment of SUI is safe and tolerable; however, more studies are needed. Gotoh *et al.* recruited 13 male patients with ASCs treatment and showed improved quality of life and that leakage volume decreased by 59.8% [39]. Choi *et al.* recruited six male patients with UI and treated them with ASCs. Improved UI and increased maximal urethral closure pressure were recorded [66]. Arjmand *et al*. recruited 10 female patients with SUI and showed a significant improvement after ASC injection at 2 weeks (P < 0.0001) and 24 weeks (P = 0.0018) [67].

Kuismanen *et al.* recruited five female patients with SUI who were treated with ASCs. At the 1-year follow-up, three patients passed the cough test and the other two patients failed it. The success rate of the procedure was 60% [40]. Garcia-Arranz *et al*. recruited nine men and 10 women with UI treated with ASCs [41]. Cells were obtained from liposuction, and intraurethral injection was performed. A total of 37.5% (n = 3) of men and 50% (n = 5) of women achieved an objective improvement of >50% and a

Table 2: Clinical trials using adipose-derived stem cells to treat stress urinary incontinence

Publication year/Author	Patients (*n*)	Cell dose (cells)	Route of injection	Number and sites of injection	Follow-up (months)	Success rate (%)
2012/ Yamamoto *et al*. [65]	3 males	2.4×10^7, 3.3×10^7, and 4.0×10^7	Periurethral and Transurethral (cystoscope guided)	5, Periurethral: Rhabdosphincter at 5 and 7 o'clock positions; Transurethral: At 4, 6, and 8 o'clock positions	6	3/3 (100)
2014/ Kuismanen *et al*. [40]	5 females	$2.5-8.5\times10^6$	Transurethral (cystoscope guided)	4, 1.5 cm distal from the urethral neck at 3 and 9 o'clock	12	3/5 (60)
2014/Gotoh *et al*. [39]	11 males	$7.3\times10^6-3.3\times10^7$	Periurethral and Transurethral (cystoscope guided)	5, Periurethral: Rhabdosphincter at 5 and 7 o´clock positions; Transurethral: at 4, 6, and 8 o´clock positions	12	8/11 (72)
2016/Choi *et al*. [66]	6 males	NA	Periurethral and Transurethral (cystoscope guided)	5, Periurethral: Rhabdosphincter at 5 and 7 o'clock positions; Transurethral: at 4, 6, and 8 o'clock positions	3	6/6 (100)
2017/ Arjmand *et al*. [67]	10 females	11.8×10^6	Transurethral and transvaginal- periurethral (urethroscope guided)	3, Transurethral: 2 and 10 o'clock positions in 0.5 cm depth of mid-urethra Periurethral: Periurethral space under concurrent urethroscopic view via transvaginal injection	6	10/10 (100)
2019/Gotoh *et al*. [68]	13 males	2.5×10^7	Periurethral and Transurethral (cystoscope guided)	4, Periurethral: Rhabdosphincter at 5 and 7 o'clock positions; Transurethral: at 4 and 8 o'clock positions	60	10/13 (76.9)
2020/ Garcia-Arranz *et al*. [41]	10 males/10 females	20×10^6 in male, 40×10^6 in female	Transurethral (cystoscope guided)	7-8, bladder neck and external sphincter		30% in male, 50% in female at 12 months

subjective improvement of >70% when compared to baseline measurements.

Limitations of most previous studies included a small sample size and the collection of only short-term results [Table 2]. The success rates ranged from 30% to 100%. Larger-scale and longer-term follow-up studies are needed to confirm the regenerative potential of ASCs for SUI treatment.

Umbilical cord blood stem cells

Lee *et al*. recruited 39 women with UI and injected UCBSCs [49]. UCBSCs were injected into the submucosal region of the proximal urethra at 4 and 8 o'clock directions at a dosage of $430 \pm 190 \times 10^6$ cells in 2 mL of medium. At the 12-month follow-up, 36% (n = 13) of patients were fully continent and 36% (n = 13) had significantly improved UI. However, 27% (n = 10) of patients experienced no improvement.

Summary of the advantages and disadvantages of the use of different types of stem cells in stress urinary incontinence treatment

MDSCs and ASCs require a biopsy, in addition to injections. As previously mentioned, the biopsy procedure may cause bleeding at the biopsy site and inflammation [59]. However, UCBSCs do not require a biopsy. MDSCs can easily differentiate into myoblasts of the same lineage [69]. ASCs and UCBSCs can also differentiate into myoblasts [70,71]. Further studies are needed to determine which stem cells have the best myoblast differentiation ability and therapeutic effects for SUI.

Adverse effects of stem-cell therapy in stress urinary incontinence treatment

During or after biopsy or injection, several morbidities may occur, including bleeding and inflammation at the biopsy site, bleeding at the injection site, as well as morphological changes including neoplasm formation, voiding difficulty, urinary retention, and urinary tract infection. Stangel-Wojcikiewicz *et al.* reported no morbidity after biopsy or injection of MDSCs [59]. Carr *et al.* reported no adverse events in their trial [58]. Among the eight patients, two women underwent midurethral tape surgery and showed that previous MDSC transplantation did not affect periurethral tissues [58]. Mitterberger *et al.* did not report any adverse events after MDSC injections [50]. Sharifiaghdas *et al*. reported that two of 10 patients developed urinary tract infections in the 1st month after MDSC injection [60]. Garcia-Arranz *et al.* reported no adverse events after ASC injections [41]. Overall, stem-cell therapy for SUI treatment is promising, with little morbidity. However, few adverse effects have been reported.

Perspectives

Stem-cell dosage

Currently, there is no consensus regarding the number of stem cells that should be administered [72]. For stroke treatment in our hospital, 2.5×10^8 stem cells are transplanted to the stroke site [73]. Previous reports regarding transplanted cells have ranged from 1×10^7 to 12×10^8 cells. The number of transplanted cells required for an effective treatment likely varies according to lesion size [72]. Similarly, in SUI treatments, the number of transplanted cells varied in different trial settings from 1×10^6 to 1.2×10^8 MDSCs [Tables 1 and 2].

Further large-scale studies are needed to determine the optimal number of cells required for transplantation.

Injection route

The most common injection sites are transurethral and periurethral sites that have been approved for safety and efficacy [Tables 1 and 2] [12]. The injection sites were at the mid-portion of the urethra around the omega-shaped rhabdosphincter [50]. Nevertheless, these injection sites require cystoscopic or ultrasound guidance [50]. Previous studies have also used a simplified method to inject the periurethra at two or three sites [53,54]. Recently, Chiang and Kuo reported using platelet-rich plasma to treat 26 female patients with SUI [74]. Platelet-rich plasma was injected into the external sphincter at five sites, with four treatments at monthly intervals. The results showed that 46.2% (n = 12) of the patients were completely dry on the pad test, and 26.9% (n = 7) of the patients maintained total continence at 12 months of follow-up. Thus, the external sphincter site may be a good choice for cell transplantation without the need for cystoscopy or ultrasound.

Number of injections

There is no consensus on the optimal number of injections for stem-cell transplantation. A previous study used 2–26 injections. More than 20 injections may be used in the previous Botox injection experience [75]. Mitterberger *et al.* reported using 15–18 portions of myoblast injection (50–100 μL/depot) and 25–30 portions of fibroblast injection (5–100 μL/depot) [56]. Stem cells have a homing ability and can move to injured sites. However, sphincter injury in patients with SUI is a chronic process and may not secrete homing signals, such as stromal-derived factor-1 [76]. Whether injected stem cells home successfully to the rhabdosphincter remains unclear. A previous trial using MSCs to treat chronic stroke also faced the same problem, which caused no improvement within 3 months [77]. The injection of cells into the external sphincter is easy. The number of injections administered may vary depending on the injection site. Large-scale trials may be required to determine the most suitable number of injections.

Conclusions

Stem-cell therapy for SUI is feasible and efficient. However, low levels of morbidity have been reported. Nevertheless, more research is needed to develop effective and minimally invasive management strategies for mild-to-moderate SUI. The efficacy, safety, and durability of autologous stem-cell injection therapy for the treatment of female SUI still require further research regarding dosage, route of injection, and number of shots. ASCs may be the most promising cell source due to a lot of fat tissue in human body, easy to harvest, and have excellent differentiation capabilities. Transurethral and transvaginal-periurethral (urethroscope guided) injection may be a preferred method of injection. The most suitable cell dosage may be 1–2.5 × 10^7 cells. To date, most clinical trials have been phase I trials studying the safety of stem-cell therapy for SUI treatment. More high-quality phase II randomized controlled trials must be conducted, so that the efficacy of stem-cell therapy for SUI treatment can be compared with other treatments, such as bulking agents.

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Conflicts of interest

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