Am J Clin Exp Urol 2026;14(1):17-33
www.ajceu.us /ISSN:2330-1910/AJCEU0169619

Review Article

Regenerative strategies for post-prostatectomy incontinence: stem cells, exosomes, and the path to clinical resolution

William Wang[1], Tarek Zaho[2], Allen Cao[3], Gopal H Badlani[4], Soroush Rais-Bahrami[4], Anthony Atala[2,4], Yuanyuan Zhang[2]

[1]*Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;* [2]*Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA;* [3]*Department of Urology, Department of Urologic Surgery, University of California, Davis, Sacramento, CA, USA;* [4]*Department of Urology, Wake Forest University School of Medicine, Winston-Salem, NC, USA*

Received October 28, 2025; Accepted January 8, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Radical prostatectomy (RP) is a highly effective treatment for localized prostate cancer; unfortunately, post-prostatectomy urinary incontinence (UI) remains a prevalent and distressing complication, significantly diminishing patients' quality of life. Current therapeutic options often provide incomplete continence restoration and may lead to substantial morbidity. This review examines the rapidly advancing field of regenerative medicine, specifically focusing on stem cell and exosome-based therapies as innovative approaches to address post-RP UI. We go deeper into the unique pathophysiology of male post-prostatectomy UI, distinguishing it from other forms of UI, and present the compelling biological rationale for these regenerative interventions. Highlighting advancements from 2014 to 2025, we explore recent preclinical and clinical progress in this domain. Furthermore, we critically assess the persistent challenges crucial for widespread clinical application, including optimizing cell dose and source, ensuring long-term efficacy and safety, and interpreting complex regulatory environments. By bridging the understanding of sex-related differences between females and males in UI and tackling the specific challenges of male post-RP incontinence, this review emphasizes that while promising, the journey from laboratory bench to bedside for these innovative therapies demands rigorous scientific inquiry and collaborative efforts.

Keywords: Stem cells, exosomes, mini-invasive therapy, post-prostatectomy urinary incontinence

Introduction

Post-prostatectomy urinary incontinence (PPI) is a significant complication of radical prostatectomy (RP) for prostate cancer (PCa) [1-3]. PCa is the second leading cause of cancer-related deaths and the most frequently diagnosed cancer in men in the United States [4]. RP, often used as the first-line treatment, even with robotic techniques, has a high incidence of PPI, affecting up to 87% of patients [1]. While most men experience resolution of post-RP urinary incontinence within 3 months [5, 6], at least one-third may endure prolonged incontinence with an observed plateau at 12 months postoperatively [7-10]. PPI severely impacts patients' quality of life, significantly affecting their physical and mental well-being, which can lead to social isolation, emotional distress, physical limitations, sleep disturbance, sexual dysfunction, and an overall burden on their lives [11-13].

Despite considerable efforts, a major challenge remains in reversing pathological changes in neuromuscular tissue and restoring urethral sphincter function for patients with PPI [14]. Multiple factors contribute to PPI, including a patient's pre-surgery anatomy, bladder function, surgical technique, and surgeon experience [15]. Urinary continence in men is maintained by proper function of the detrusor smooth muscle, the proximal intrinsic sphincter at the bladder neck, the urethral suspensory mechanism (pubo-urethral ligaments), and the external urethral sphincter (EUS) electromyog-

https://doi.org/10.62347/MBLA4964

raphy (EMG) innervated by the pudendal nerve [16-18]. Several surgical factors following RP, including dissection during surgery, neurovascular bundle damage, muscle atrophy, postoperative inflammation and fibrosis, and can all negatively impact continence [19]. These surgical factors reduce the number of functional nerve fibers and hinder potential regenerative efforts, as newly formed fibers are often less effective. Furthermore, inflammatory responses and peri-neural fibrosis around nerves further impede nerve recovery and function. Denervation additionally triggers muscle atrophy, a decrease in muscle mass, and function within the sphincter [20]. Fibrosis within the muscle tissue further diminishes elasticity and function, with scar tissue replacing healthy muscle and leading to overall incontinence [21].

The combined effects of neuromuscular (NM) impairment result in decreased urethral pressure, weakening the continence mechanism. This manifests as increased urgency, frequency of involuntary leakage, and a particular vulnerability during activities that increase intra-abdominal pressure [19, 22]. Despite existing treatment options like rehabilitation, slings, and artificial urinary sphincter (AUS) implants, no perfect solution currently exists for PPI [23]. AUS is considered the most effective treatment for this condition; however, most men still require at least one pad daily [23-25]. In addition, complications such as device malfunctions, urethral erosion, urinary retention, temporary pain, and infection can occur, leading to revision surgeries in up to 80% of cases within 10 to 15 years [20, 26-28]. This highlights the critical need for novel therapeutic strategies to promote NM regeneration, restore urethral sphincter function, and ultimately improve patients' quality of life by addressing significant psychological and social repercussions of PPI.

Sex-related differences in urinary incontinence: implications for regenerative therapies

While the goal of restoring continence is shared, the anatomical, physiological, and etiological distinctions between male and female UI demand tailored approaches in diagnosis, conventional management, and the application of regenerative medicine. Understanding these sex-related differences is crucial for developing effective therapies, particularly in emerging fields like stem cell and exosome therapy. The anatomical differences between male and female pelvic structures that influence continence mechanisms are illustrated in **Figure 1**.

PPI is mainly an iatrogenic complication of prostate cancer surgery, arising from a combination of structural and neurologic factors. The leading cause is direct injury to continence mechanisms during surgery [19, 28]. This includes damage to the external urethral sphincter (EUS) [29], either mechanical trauma or loss of blood supply, which impairs voluntary sphincter control [19, 30]. Concurrently, injury to the pudendal and pelvic nerve plexus, including cavernous nerves, further reduces autonomic and somatic input, weakening sphincter tone and reflex control [18, 31]. In addition, loss of intrinsic urethral smooth muscle function and reduced urethral support from disruption of structures such as the puboprostatic ligaments contribute to impaired continence [19, 28]. Furthermore, postoperative issues like bladder neck scarring and new-onset detrusor dysfunction can also occur, leading to persistent, often mixed-type urinary incontinence [34].

Stem cell and exosome therapies have been extensively researched for female UI [34-36]. A comprehensive comparison of the pathophysiology, rationale, treatment strategies, and associated challenges between female and male UI could greatly facilitate the advancement of these regenerative approaches, particularly for male UI conditions including post-prostatectomy incontinence (PPI). This review highlights these critical differences, paving the way for more targeted and successful regenerative interventions in both sexes (**Table 1**).

Pathophysiology of post-radical prostatectomy urinary incontinence in males

Understanding the complex causes of post-RP UI in males is essential for developing targeted regenerative therapies. RP can cause UI through disrupting several mechanisms required for urinary continence. During RP [19, 29], surgical removal of the prostate can cause external urethral sphincter (EUS) injury due to of direct surgical trauma [30, 32], thermal injury, or ischemia that can result in fibrosis (scarring), atrophy and loss of functional muscle fibers [50]. Another key factor causing post-RP UI is pudendal nerve injury. Traction, compression, or cutting of the nerves during surgery can

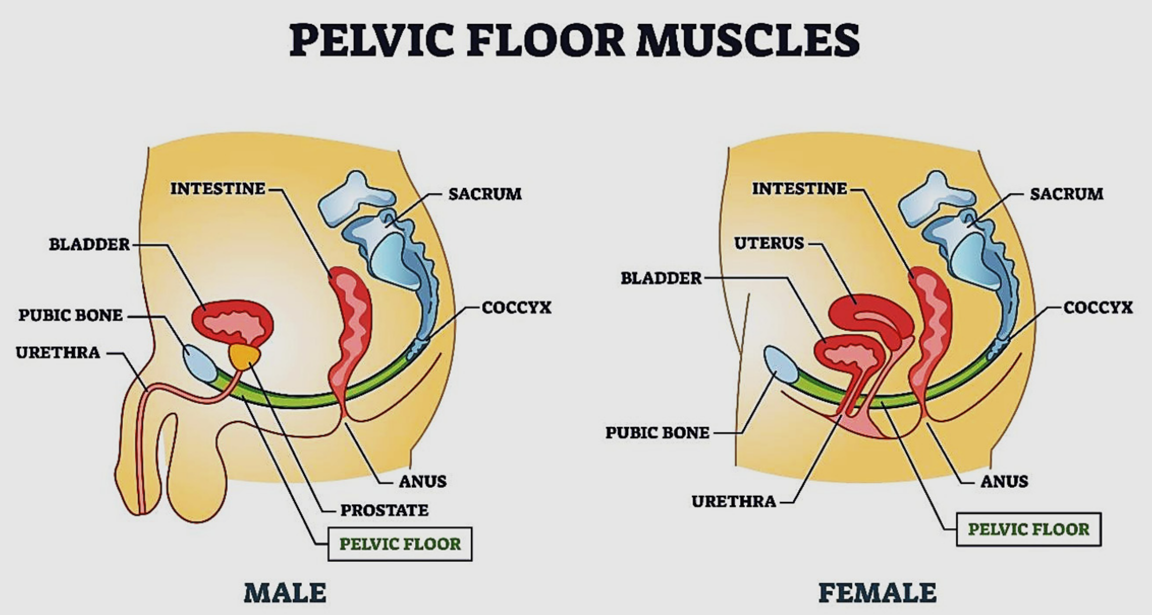

Figure 1. Comparison of male and female pelvic floor musculature and organ anatomy. This diagram illustrates the sagittal view of the male and female pelvis, highlighting the position of the pelvic floor muscles relative to urogenital and digestive organs. Key anatomical structures labeled include the bladder, urethra, pubic bone, sacrum, coccyx, intestine, and anus. The male pelvis features the prostate gland located beneath the bladder, while the female pelvis contains the uterus situated between the bladder and rectum. These anatomical differences underpin varied susceptibilities to urinary incontinence. In males, the prostate's position and the longer urethral length contribute to continence, with prostatectomy often disrupting these structures, leading to post-surgical incontinence. In females, the shorter urethra, wider pelvic outlet, and direct anatomical relationships with the reproductive organs (e.g., uterus) predispose to stress incontinence, particularly after childbirth or with hormonal changes. The pelvic floor muscles support these organs in both sexes, and their functional integrity is paramount for maintaining continence.

result in denervation, leading to EUS atrophy. Removing the prostate also causes bladder neck incompetence because it inherently disrupts the internal urethral sphincter mechanism, which normally helps with continence [18, 31]. Pelvic floor dysfunction is an additional mechanism because the surgery can impact on the integrity and neuromuscular control of the pelvic floor, further contributing to muscle weakness [19, 28]. Furthermore, post-surgical inflammation and the formation of scar tissue can significantly impair sphincter function. Fibrosis and inflammation can make regeneration more difficult. Effective regenerative therapies will need to address the above key factors responsible for post-RP UI [36].

Rationale for stem cell and exosome therapy in post-RP UI

Stem cells and exosomes-based therapy have been identified to have the potential to resolve major defects responsible for post-RP UI. Damage to the external urethral sphincter (EUS) may be repaired through the regenerative capacity of stem cells, which can differentiate into muscle and nerve lineages to restore both structural integrity and functional control [33, 40, 48]. This could potentially restore the structural integrity and function of the EUS and its innervation. In addition, stem cells and exosomes can help regulate inflammation and tissue scarring, as both possess strong immunomodulatory and anti-fibrotic properties that may limit the adverse effects of postoperative healing [33, 42]. These therapies could promote angiogenesis by encouraging the formation of new blood vessels and therefore improve blood supply to the damaged urethral sphincter, improving oxygen and nutrient delivery to injured tissues, and enhancing tissue viability and regeneration [36, 49]. Beyond muscle and vascular repair, stem cells and exosomes contribute to nerve healing. Stem cells and exosomes can produce and release neurotrophic factors, which are crucial for promoting nerve regrowth and re-innervation of the EUS [34]. Finally, stem cells and exosomes can exert

Table 1. Differences in pathophysiology, rationale, treatment strategy, and challenges between female and male urinary incontinence

Aspect	Female UI	Male UI (Post-RP Focus)
Primary Etiology	Childbirth, menopause, aging (stress UI); idiopathic or neurogenic (urge UI) [37].	Iatrogenic surgical trauma to external urethral sphincter and pudendal nerves [38].
Core Pathophysiology	Pelvic-floor and sphincter weakness; fascial laxity; detrusor overactivity [39].	Sphincter injury, fibrosis, denervation, bladder-neck incompetence [38].
Anatomical Target	Intrinsic urethral sphincter; periurethral and pelvic-floor tissues [37].	External urethral sphincter and pudendal nerve [38].
Regenerative Goal	Restore muscle strength, connective-tissue integrity, and neural support [40].	Regenerate striated sphincter, promote re-innervation, reduce fibrosis [40].
Cell Types Studied	ADSCs, MDSCs, BM-MSCs, USCs, ESCs [34, 41, 43, 55].	ADSCs, MDSCs, BM-MSCs, USCs [34, 41, 43, 55].
Exosome Action	Pro-regenerative, anti-inflammatory, pro-angiogenic effects [44].	Pro-myogenic, neurotrophic, anti-fibrotic effects [44].
Delivery Route	Periurethral/transurethral/pelvic-floor injection [45].	Direct sphincter injection (transperineal/transrectal) [45].
Therapeutic Challenges	Diffuse injury, mechanical stress, limited cell integration [38].	Localized fibrosis, neural repair complexity, oncologic caution [37].
Conventional Surgery	Mid-urethral sling; bulking agents [46].	Artificial urinary sphincter; male sling; bulking agents [46].
Impact on Quality of Life	Significant, affects social, physical, and psychological well-being.	Highly significant, often leading to severe distress, social isolation, and impacts on body image.

Abbreviations: ADSCs = Adipose-Derived Stem Cells, MDSCs = Muscle-Derived Stem Cells, BM-MSCs = Bone Marrow-Derived Mesenchymal Stem Cells, USCs = Urine-Derived Stem Cells, ESCs = Embryonic Stem Cells; AUS = Artificial Urinary Sphincter, UI = urinary incontinence.

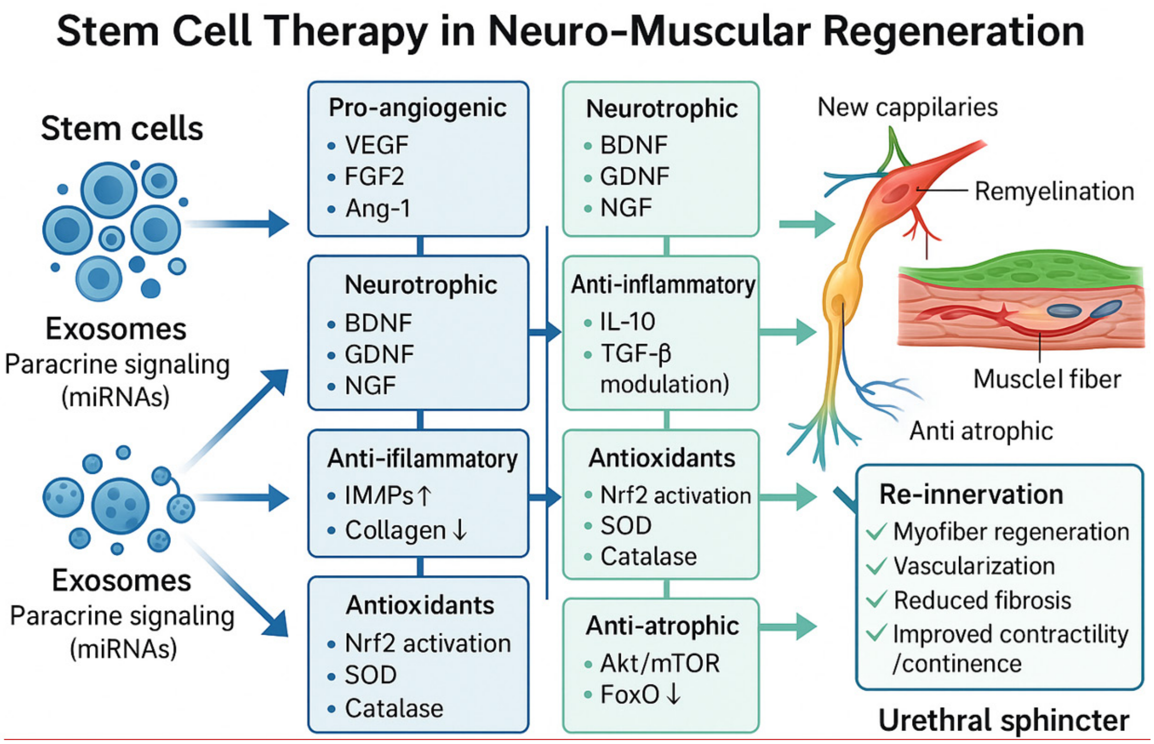

Figure 2. Multifaceted mechanism of stem cell therapy in neuro-muscular regeneration, particularly emphasizing its application in the urethral sphincter. Stem cells and their secreted products, Exosomes (carrying miRNAs), exert their therapeutic effects through several critical pathways. These include pro-angiogenic signaling (using factors like VEGF and FGF2) to promote new blood vessel growth, neurotrophic support (via BDNF, GDNF, and NGF) for nerve health, and strong anti-inflammatory and antioxidant actions (reducing fibrosis and countering oxidative stress with SOD and Catalase). Additionally, they have an anti-atrophic effect, preventing muscle wasting. The combined result of these actions is the formation of new capillaries, remyelination of nerve fibers, and ultimately Re-innervation, leading to tangible clinical benefits in the urethral sphincter such as myofiber regeneration, reduced fibrosis, and improved contractility/continence.

paracrine effects, even without directly differentiating into new cells. Stem cells and exosomes secrete a wide array of growth factors, cytokines, and microRNAs. These molecules act as messengers, stimulating the body's own repair mechanisms in surrounding cells [42, 51]. Considering the above potential benefits from stem cells and exosomes, efforts have been made to explore the stem cell and exosome therapy for the treatment of post-RP UI. The mechanism reported link benefits to paracrine signals such as VEGF and BDNF, antioxidant pathway activation, and reduced inflammatory markers demonstrated in **Figure 2**.

Stem cell-based therapies: promising horizons

Types of stem cells explored

One important question regarding stem cell therapy of post-RP UI is the identification of suitable types of stem cells. Several types of stem cells have been tested in various preclinical post-RP UI models. These cells include adipose-derived stem cells (ADSCs), muscle-derived stem cells (MDSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), induced pluripotent stem cells (iPSCs), and urine-derived stem cells (USCs). A comparison of various stem cells will be helpful for determining the optimal source(s) of stem cells for the treatment of post-RP UI [34, 41, 42, 52].

ADSCs also called adipose-derived mesenchymal stem cells [60, 61] or adipose-derived stromal cells [62], are derived from fat tissue and are abundant and easily accessible. These cells were positive with sCD34 and CD44 [63]. These cells produced fibroblastic colonies that express smooth muscle cell markers, including alpha-smooth muscle actin, calponin, and desmin [66]. In addition, these cells were able to secrete cytokines associated with angiogenesis, including vascular endothelial growth factor-A, angiopoietin-2, and placental growth factor. These characteristics make ADSCs potentially suitable for regenerating functional urethral sphincter muscle [56, 57].

Muscle-derived stem cells (MDSCs) are derived from skeletal muscle, a very convenient and plentiful source. MDSCs exhibit a high myogenic capacity and play an important role in muscle regeneration [58]. MDSCs are multipotent and can differentiate into various cell types, including muscle cells. Furthermore, these cells can secrete various trophic factors that can promote endogenous tissue repair. Thus, MDSCs are particularly relevant for EUS repair [58, 59].

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are well-characterized. These multipotent cells are capable of tissue repair and have immunomodulatory properties [60, 61]. The BM-MSCs are accessible because they can be isolated from different bone sources, and they can be cultivated and expanded in vitro in multiple cell types [62]. Therefore, BM-MSCs represent a promising treatment option for post-RP UI.

Induced pluripotent stem cells (iPSCs) were initially reported by Takahashi et al. In their breakthrough study, iPSCs were generated by introducing four specific transcription factors: Oct4, Sox2, Klf4, and c-Myc into adult mouse fibroblasts [63]. These cells exhibited the morphology and growth properties of embryonic stem (ES) cells and expressed marker genes for ES cells. The research team subsequently extended their research using human fibroblast cells [64]. Ectopic expression of the same set of four genes resulted in reprogramming of the fibroblasts into pluripotent stem cells. A major advantage of iPSCs for regenerative therapies is that these cells offer the potential for patient-specific cell sources, eliminating the ethical concerns associated with embryonic stem cells. However, using iPSCs in regenerative therapy faces challenges related to potential tumorigenicity and controlled differentiation [65, 66].

Urine-derived stem cells (USCs) are a subpopulation of cells from urine exhibiting progenitor cell features and the potential to differentiate into several bladder cell lineages expressing urothelial, smooth muscle, endothelial, and interstitial cell markers [67, 68]. Importantly, USCs maintained a normal karyotype after serial culture. An advantage of USCs is that they provide an alternative source for post-RP UI [68].

Preclinical progress

Stem cell-based tissue repair therapies have been evaluated functionally, histologically, cellularly, and molecularly in numerous preclinical studies. These studies have consistently demonstrated promising results with stem cell therapies in multiple animal models relevant to UI and revealed multiple mechanisms by which stem cells can stimulate tissue repair.

Stem-cell-based therapies have improved leak point pressure (LPP) and continence rates. In a rabbit model of urinary incontinence via sphincterotomy, endoscopic implantation of cultured autologous myoblasts (CAM) was tested as a therapy [69]. The leak-point pressure (LPP) was significantly improved in the animals receiving CAM implantation as compared to the control group, and the improvement was detected throughout the evaluation period. In a freeze injury model of post-surgical intrinsic sphincter deficiency-related urinary incontinence, the leak point pressure of autologous bone marrow-derived cell-implanted rabbits is significantly higher than that of cell-free implanted controls [41]. In a rat model of post-RP UI, mesenchymal stem cell (MSC) administration also significantly improved urinary continence [70].

Histological analysis showed that stem cell therapies increased muscle fiber density, reduced fibrosis, and enhanced vascularity in the EUS. In the rabbit model of UI via sphincterotomy, interconnected islands were formed by muscle fibers in the CAM-treated sphincters [68]. BMSC and ADSC were reported to reduce fibrosis and enhance angiogenesis in rodent models [71, 72].

The functional and morphological effects of stem cell therapies are associated with the detection of transplanted cells in the target tissues and their differentiation into muscle-like or nerve-like cells. Stem cells are chosen for tissue repair because of their ability to undergo multilineage differentiation and self-renewal [73]. Transplanted syngeneic and heterotopic adipose-derived mesenchymal stem cells were able to survive after the injection into the rat sphincter [74]. In another rat model of UI, injected skeletal muscle-derived mononuclear cells (SMDMCs) were incorporated into the urethra to promote histological recovery of the injured urethral sphincter [75]. In a rabbit model, urine-derived stem cells (USC) exhibited strong proliferative potential and the capability to differentiate into multiple types of cells, including urothelial, myogenic, and osteogenic lineages [76]. In a mouse UI model via bilateral pudendal nerve transaction, non-invasive cell tracking confirmed nerve regeneration and neuromuscular junction formation in vivo, and the stem cell differentiation was associated with the expression of neuronal markers and acetylcholine receptor [47].

The efficacy of stem cells in tissue repair can be further enhanced by their upregulation of pro-regenerative growth factors and downregulation of inflammatory markers. Administration of human mesenchymal adipose-derived stem cells repaired tissue damage through tissue-specific paracrine mechanisms in a rat model mimicking radical prostatectomy [77]. These stem cells not only released soluble growth factors but also activated the secretome of the recipients. In a rat model of UI, administration of muscle-derived stem cells significantly lowered the inflammation rate as compared to the control group [78]. A summarization of these studies is illustrated in (**Table 2**).

Clinical translation and recent advancements (2024-2025)

Early-phase clinical trials have begun to explore the safety and potential effectiveness of stem cell injections. In a phase 1 clinical trial, a single intracavernous injection of autologous adipose-derived stem cells was safe in patients following radical prostatectomy [83]. In another phase I study, transurethral injection of autologous adipose-derived stem cells was demonstrated to be safe and effective for the treatment of urinary incontinence after radical prostatectomy [90]. Urine leakage volume was improved with time in all the treated patients in the 24-h pad test, along with subjective symptoms and quality of life. In a randomized, double-blind, crossover, placebo-controlled, phase 1/2a clinical trial, a single dose administration of Wharton jelly mesenchymal stromal cells (WJ-MSCs) in patients with chronic complete spinal cord injury (SCI) was safe, with no significant side effects [41]. WJ-MSC infusion significantly improved pinprick sensation in the dermatomes below the level of injury compared with placebo.

In addition, the treatment induced other clinically relevant effects, including elevated bladder maximum capacity and compliance and reduced bladder neurogenic hyperactivity and external sphincter dyssynergy at the individual level. In two phase I/II clinical trials, the safety and feasibility of autologous adipose-derived mesenchymal stem cells (ADSCs) were tested in the treatment of urinary incontinence after radical prostatectomy in men or female stress urinary [85]. These two trials showed that intraurethral application of ADSCs is safe and feasible for the treatment of urinary incontinence after radical prostatectomy or in female stress urinary incontinence. In a recent randomized phase II clinical trial in 32 patients with traumatic complete spinal cord injury (SCI)-induced neurogenic bladder, including treatment and control arms, the combined administration of autologous bone marrow-derived mesenchymal stem cells (BMSCs) and Schwann cells (SCs) significantly improved the urodynamic study parameters, urinary incontinence rate, and incontinence quality of life [86]. These early clinical studies demonstrated the potential of using stem cell therapy for patients with UI.

While multiple reports suggest feasibility and a favorable safety profile with some improvements in continence, several challenges remain. The mechanism of action of stem cells injected into the lower urinary tract and the viability of the injected cells are not clear, and the optimal timing of stem cell therapy remains to be determined [87]. The following additional issues will need to be resolved in order to facilitate the development of effective stem cell therapy of post-RP UI [88]: (1) Cell source and quality control: Standardizing the isolation, expansion, and characterization of cells is crucial to ensure consistent therapeutic potency. (2) Optimal cell dose and delivery method: Determining the ideal number of cells and the most effective way to deliver them (e.g., direct EUS injection, periurethral, intravenous) is vital. (3) Cell survival and engraftment: Ensuring the long-term survival and functional integration of transplanted cells is a key hurdle. (4)

Table 2. Pre-clinical studies on stem cell therapy for urinary incontinence

Study	Animal Model	Cell Type/Source	Cell Dose, Injection, and Route	Key Findings/Outcomes
Yiou et al. [77]	Male SD rats	(MPCs)	-5×10^{6} cells/10 μL - Periurethral injection	41% restoration of sphincter function at 1 month on urodynamic testing
Cannon et al. [78]	Female SD rats	(MDPCs)	-3×10^{6} cells/20 μL - Injected at 2 and 10 o'clock periurethral sites	- Fast-twitch contractions improved to 87% of normal. - Abundant new muscle fiber formation. - Minimal inflammation.
Lim et al. [79]	Female SD rats	(UCBMC)	- 2×10^{6} cells/20 μL - Each side of mid-urethra	- Mean LPP ↑ - Sphincter muscle restored
Corcos et al. [80]	Female SD rats	(MPCs)	- 0.5×10^{6} cells/20 μL - Periurethral injection at 3 and 9 o'clock	- Mean LPP ↑ - IF staining: MHC +/desmin +
Eberli et al. [81]	Female beagle dogs	Autologous muscle precursor cells	-5×10^{7} cells/mL - 2 mL injected at multiple sphincter sites	- Sphincter pressure restored to ~80% of normal. - Reinnervated muscle fibers
Raffo et al. [68]	Male New Zealand rabbits	Autologous myoblasts (CAM)	- Myoblasts resuspended in platelet-poor plasma (PPP) - Endoscopic injection to sphincter region	- Mean LPP ↑ - Histology showed: muscle fibers restoration in treated Gp, vs fibrosis in control Gp

Abbreviations: SD = Sprague-Dawley, MOCs = Mesenchymal precursor cells, MDPCs = Muscle-derived progenitor cells, UCBMC = umbilical cord blood mononuclear cells, PPP = platelet-poor plasma, LPP = leak point pressure, Gp = Group.

Immunogenicity: Although mesenchymal stem cells (MSCs) are generally considered immune-privileged, potential immune rejection remains a concern for allogeneic (donor) cells. (5) Tumorigenicity: A theoretical risk, particularly with iPSCs, requires rigorous preclinical safety evaluations. (6) Ethical and regulatory hurdles: Navigating complex ethical considerations and stringent regulatory pathways for cell-based therapies is a significant challenge.

A summarization of these studies is illustrated in (**Table 3**).

Exosome therapy: emerging opportunities

Exosomes as the "next generation" therapy

Exosomes are tiny (nanoscales, ranging from 30 to 150 nm) extracellular vesicles secreted by various cells, including stem cells. They carry a diverse cargo of proteins, lipids, mRNA, and microRNAs, acting as crucial mediators of intercellular communication. These vesicles have regenerative, anti-fibrotic, pro-angiogenic, anti-apoptotic, anti-inflammatory, and anti-hypoxic properties [44, 88]. Thus, exosomes have the potential to stimulate tissue regeneration, restore urethral function, and repair the damaged nerves and muscles, therefore alleviating symptoms and enhancing the quality of life of the patients [42]. The characteristics position exosome therapy to become a potential new treatment for UI. In addition, exosomes offer several advantages over whole-cell therapies. Exosomes are less likely to trigger an immune response due to their cell-free nature [95]. Storage and transportation of exosomes are easier compared to live stem cells [42]. The risk of exosome therapy to induce tumor formation or uncontrolled proliferation appears to be low. Due to their small sizes, exosomes can cross biological barriers more readily [42, 94]. Furthermore, ethical concerns of exosome therapies are reduced compared to those associated with stem cell therapies.

Mechanisms of action

Exosomes derived from stem cells (e.g., ADSC-Ex, MSC-Ex) are believed to exert therapeutic effects through multiple mechanisms [42, 95]. A major mechanism is paracrine signaling. Exosomal delivery of pro-regenerative cargo to recipient cells can stimulate the body's own repair mechanisms. Another mechanism is modulating immune responses to reduce tissue damage, because of their anti-inflammatory and immunomodulatory effects [42]. Exosomes are known to promote angiogenesis, a process of new blood vessel formation, in tissue repair [95]. Exosomes can exert neuroprotection and stimulate neurogenesis because they support the survival and growth of neurons. Since exosomes can deliver microRNAs that inhibit pathways leading to scar tissue formation, exosomes can also reduce fibrosis [42, 96]. Through the above mechanisms, exosomes have great potential to promote tissue regeneration and functional recovery in patients with UI.

Preclinical progress and opportunities

Preclinical studies using exosome therapy in cell-based and animal models of UI have shown promising results, including improved urethral sphincter function, reduced fibrosis and inflammation, increased muscle content and nerve regeneration, and enhanced tissue viability and structural integrity [42]. Multiple in vitro studies showed that exosomes derived from adipose-derived mesenchymal stem cells (ADSCs) can regulate extracellular matrix (ECM) remodeling via enhancing collagen expression in primary fibroblasts of stress urinary incontinence [54, 96]. Since ECM remodeling is essential to the pathology of SUI, these exosomes may provide a potential therapeutic approach for SUI. In another study, bone marrow mesenchymal stem cell-derived small extracellular vesicles (BMMSC-sEVs) were able to promote collagen synthesis and improve the function of the damaged urethral sphincter in a SUI rat model [96]. Also in rat SUI models, treatment with urine-derived stem cell exosomes significantly improved the urodynamic parameters, with good recovery of the injured muscle tissues [42, 49, 97]. The preclinical findings from different research groups provide a basis for further exploring exosome treatment of SUI. A summarization of some preclinical cases is illustrated in (**Table 4**).

Persistent challenges and future directions

Stem cell therapy for patients with SUI holds promise, but not for PPI in PCa. There is a big concern that implanted stem cells might stimulate the regrowth of residual PCa cells [98].

Table 3. Clinical trial studies investigating stem cell therapy for male sphincter dysfunction

Study	Cell Type	No. and site of Injections	Pat Cohort	Cell Dose/Frequency	Primary Outcome	Outcomes	Adverse Events
Garcia-Arranz et al. [41]	Autologous Adipose-Derived MSCs	- Two sessions - Endoscopic intraurethral injection	I/II, PP SUI	20×10^6 ASCs after no improvement in 3 months 40×10^6	Safe and feasible	- LPP: NR - Continence: 3/8 (37.5%) achieved >50% - Pad-test ↓.	None reported during 12-month follow-up
Gotoh et al. [88]	Autologous ADRCs	- Single session - Periurethral/rhabdo-sphincter injection	Clinic-al (long-term follow-up), N=13	-1×10^7 cells	Long-term efficacy and safety	- LPP: NR - Continence: 10/13 (76.9%) improved in 55-72 months. - Pad-test ↓.	No significant AEs; no PSA rise
Choi et al. [83]	Autologous ADRCs	- Single session - Trans-urethral injection	I, N=10	NR	Safe and feasible	-LPP: NR - Continence: improved in all patients - MUCP ↑ 44.0 → 63.5 cmH_2O at 12 weeks. - Pad-test ↓.	No significant AEs reported
Gotoh et al. [89]	Autologous ADRCs	- Single session - Periurethral	Clinic-al study, N=11 (male SUI)	Differ between one patient to another with a range between 7.5×10^6-3.3×10^7	NR	-LPP: NR - Continence: 1/11 fully continent at 1 year; 8/11 ↑ - MUCP ↑ 35.5 → 44.7 cmH_2O.	No significant AEs reported
Yamamoto et al. [90]	Autologous ADRCs	- Single session (two injections at different sites) - Periurethral	Initial case report, N=3 (male SUI)	NR	Safe and feasible	- LPP: NR - Continence: overall improvement - MUCP ↑.	No significant AEs reported
Yamamoto et al. [91]	Autologous ADSCs	- Single session (two injections at different sites) - Periurethral	Initial case report, N=2 (male SUI)	1×10^7 cells	Safe and feasible	LPP: NR; Continence: subjective improvement; MUCP and functional profile length increased (study later retracted).	No significant AEs reported

Abbreviations: ADRCs = Adipose-Derived Regenerative Cell; ADSCs = Adipose-Derived Stem Cells; MSCs = Mesenchymal Stem Cells; SUI = Stress Urinary Incontinence; LPP = Leak-Point Pressure; MUCP = Maximum Urethral Closing Pressure; AE(s) = Adverse Event(s); NR = Not reported; PSA = Prostate-specific antigen.

Table 4. Exosome-based therapies for sphincter dysfunction (Preclinical Studies)

Study	Exosome Source	Dose	Production/Characterization Notes	Animal Model & Injection Site	Key Outcomes
Rolland et al. [96]	Platelet-derived exosomes (PEP)	1×10^{12} exosomes/ml	- Platelet additive medium (PAS III M); - Exosome pellets fixed for TEM imaging. - SP-IRIS and AFM for structural analysis.	- Female Yorkshire-cross pigs - Peri/intrasphincter injection with collagen carrier	- Restoration of urethral sphincter function. - ↑ urethral pressures by Day 42. - Muscle regeneration at sphincter site.
Wu et al. [84]	USC-derived exosomes	1×10^{10} exosomes/ml	Exosome pellets fixed for TEM.	- Female SD rats - Injections in pubococcygeus muscle	- ALPP and MBV improved. - Sphincter functional recovery consistent.

Abbreviations: PEP = Platelet-derived exosomes; USC(s) = Urine-derived stem cell(s); ALPP = Abdominal leak-point pressure; MBV = Maximum bladder volume; NTA = Nanoparticle tracking analysis; TEM = Transmission electron microscopy; SP-IRIS = Single particle interferometric reflectance imaging sensor; AFM = Atomic force microscopy; SUI = Stress urinary incontinence.

Exosomes, extracellular vesicles carrying proteins, mRNA, and miRNA, offer several advantages over whole stem cells for therapy [93, 99, 100], including protein protection, easy cell membrane penetration, allogeneic compatibility, no mal-differentiation risk, and easy storage. Besides urine-derived stem cells (USCs), USC-derived exosomes (uEx) have shown promise in promoting skeletal muscle regeneration and improving sphincter function in a female rat urinary incontinence (UI) model. However, while exosome therapy holds potential for SUI [75], its application for PPI remains uncharted.

An optimal PPI treatment strategy would involve minimally invasive post-operative interventions to restore urethral sphincter function while inhibiting residual cancer cell regrowth. Early and effective promotion of nerve regeneration, inhibition of excessive fibrosis, and improved muscle function are critical for preventing PPI by restoring NM communication. Furthermore, although RP achieves excellent results in the primary treatment of PCa, a significant proportion (20-50%) of patients experience biochemical recurrence after RP [101-103], characterized by an increase in serum prostate-specific antigen, indicating that the PCa may not have been eradicated or may have returned. Thus, to address the risk of PCa recurrence, immediate blockade of pathological angiogenesis to malignant cells after RP is critical. Therefore, developing optimal strategies that simultaneously promote nerve regeneration, support muscle health, and block abnormal angiogenesis is crucial for effective PPI treatment immediately after RP.

Despite their promise, major challenges remain. There are no standardized protocols for stem cell or exosome isolation, expansion, and characterization [104, 105]. Stem cells and exosomes derived from different sources may need to be prepared differently [78]. Optimization and standardization of isolation, expansion, and characterization of stem cells and exosomes will be crucial for ensuring their consistent potency and viability across different batches [106].

Optimal dosing and delivery also require definition, as insufficient doses may be ineffective, whereas excessive doses may cause adverse effects including inflammation, fibrosis, immune reactions, infection, or theoretical tumorigenesis [107-109]. Approaches to determining the ideal number of stem cells and exosomes for the treatment will need to be developed. Injection techniques will also need to be optimized for precision, retention, and proper distribution within the target tissue [106].

Immunogenicity and tumorigenicity remain concerns, particularly for allogeneic cells and pluripotent stem sources; exosomes may also carry tumor-promoting or tumor-suppressive signals depending on their origin [94, 110]. Regulatory complexity, production cost, and the need for large, multi-center trials represent further barriers. Future directions may include combination strategies, where exosomes provide rapid effects and stem cells offer sustained benefits, as well as engineering both products to enhance regeneration and limit regression of restored tissues [42, 111].

For stem cell and exosome therapies to be used in patients with post-RP UI, it will be necessary to meet regulatory requirements and to have an effective commercialization plan. Strict regulatory pathways for cell and gene therapies make the development complex and lengthy. The high cost of stem cell and exosome production and clinical trials can be a barrier to widespread adoption. Need for large-scale, multicenter randomized controlled trials to establish definitive efficacy and safety represents another major challenge [110]. It will be essential to define the success metrics for stem cell and exosome therapies. Future studies will need to move beyond simply measuring pad weight to include patient-reported outcomes and quality of life assessments, which is ultimately important.

Conclusion

Stem cell and exosome-based therapies represent a transformative frontier in the treatment of urinary incontinence after radical prostatectomy. Preclinical evidence strongly supports their potential to regenerate damaged tissues, modulate inflammation, and restore sphincter function. Early-phase clinical trials offer cautious optimism. Exploration of stem cell and exosome-based therapies for post-RP UI will benefit from the knowledge gained in regenerative therapies of female patients. Reciprocally, knowledge acquired in the development of regenerative therapies for post-RP UI may facilitate stem cell and exosome therapy for female UTI patients.

Significant challenges remain in optimizing cell sources, delivery strategies, ensuring long-term efficacy and safety, and establishing standardized manufacturing processes. Rigorous scientific investigation, well-designed clinical trials, and close collaboration between researchers, clinicians, and regulatory bodies are paramount to translate the promise of regenerative medicine into a tangible and widely accessible therapeutic reality for the many men suffering from post-prostatectomy UI. The journey is complex, but the potential to profoundly improve patients' quality of life provides a powerful impetus for continued research and innovation in this exciting field.

Acknowledgements

The authors would like to acknowledge funding supports Federal funds from DoD, Idea Development Award HT94252510856 (PI: Y. Z.).

Disclosure of conflict of interest

None.

Address correspondence to: Yuanyuan Zhang, Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA. E-mail: Yuanyuan.Zhang@Advocatehealth.org

References

[1] Gacci M, De Nunzio C, Sakalis V, Rieken M, Cornu JN and Gravas S. Latest evidence on post-prostatectomy urinary incontinence. J Clin Med 2023; 12: 1190.
[2] Urkmez A, Ranasinghe W and Davis JW. Surgical techniques to improve continence recovery after robot-assisted radical prostatectomy. Transl Androl Urol 2020; 9: 3036-3048.
[3] Razdan S, Pandav K, Altschuler J, Moody K, Martin L, Patel HD, Mohamed N, Dovey Z and Tewari AK. Impact of exercise on continence in prostate cancer patients post robotic assisted radical prostatectomy: a systematic review. Am J Clin Exp Urol 2023; 11: 320-327.
[4] Screening for prostate cancer. New England Journal of Medicine Accessed October 19, 2025. https://www.nejm.org/doi/full/10.1056/NEJMcp2209151?utm_source=openevidence.
[5] Hoyland K, Vasdev N, Abrof A and Boustead G. Post-radical prostatectomy incontinence: etiology and prevention. Rev Urol 2014; 16: 181-188.
[6] Holze S, Mende M, Healy KV, Koehler N, Gansera L, Truss MC, Rebmann U, Degener S and Stolzenburg JU. Comparison of various continence definitions in a large group of patients undergoing radical prostatectomy: a multicentre, prospective study. BMC Urol 2019; 19: 70.
[7] Braun AE 3rd, Washington SL, Cowan JE, Hampson LA and Carroll PR. Impact of stress urinary incontinence after radical prostatectomy on time to intervention, quality of life and work status. Urology 2023; 180: 242-248.
[8] Rodriguez E Jr, Skarecky DW and Ahlering TE. Post-robotic prostatectomy urinary continence: characterization of perfect continence versus occasional dribbling in pad-free men. Urology 2006; 67: 785-788.
[9] Storås AH, Sanda MG, Garin O, Chang P, Patil D, Crociani C, Suarez JF, Cvancarova M, Loge JH and Fosså SD. A prospective study of patient reported urinary incontinence among American, Norwegian and Spanish men 1 year after prostatectomy. Asian J Urol 2020; 7: 161-169.
[10] Anding R, Comiter C, Tse V and Hübner W. Current surgical management of postprostatectomy incontinence - workup, options and decision making. Continence 2023; 8: 101044.
[11] Jaunin-Stalder N and Lagro-Janssen AL. Urinary incontinence: neither men nor women should be forgotten. Rev Med Suisse 2013; 9: 1535-1537.
[12] Broome BA. The impact of urinary incontinence on self-efficacy and quality of life. Health Qual Life Outcomes 2003; 1: 35.
[13] Trofimenko V, Myers JB and Brant WO. Post-prostatectomy incontinence: how common and bothersome is it really? Sex Med Rev 2017; 5: 536-543.
[14] White AJ, Reeve BB, Chen RC, Stover AM and Irwin DE. Urinary incontinence and health-related quality of life among older Americans with and without cancer: a cross-sectional study. BMC Cancer 2013; 13: 377.
[15] Averbeck MA, Marcelissen T, Anding R, Rahnama'i MS, Sahai A and Tubaro A. How can we prevent postprostatectomy urinary incontinence by patient selection, and by preoperative, peroperative, and postoperative measures? International consultation on incontinence-research society 2018. Neurourol Urodyn 2019; 38 Suppl 5: S119-S126.
[16] Cruz Y, Pastelín C, Balog BM, Zaszczurynski PJ and Damaser MS. Somatomotor and sensory urethral control of micturition in female rats. Am J Physiol Renal Physiol 2014; 307: F1207-F1214.
[17] Damaser MS, Broxton-King C, Ferguson C, Kim FJ and Kerns JM. Functional and neuroanatom-

ical effects of vaginal distention and pudendal nerve crush in the female rat. J Urol 2003; 170: 1027-1031.

[18] Maher S, Gerber D, Balog B, Wang L, Kuang M, Hanzlicek B, Malakalapalli T, Van Etten C, Khouri R Jr and Damaser MS. Contribution of pudendal nerve injury to stress urinary incontinence in a male rat model. Sci Rep 2024; 14: 7444.

[19] Heesakkers J, Farag F, Bauer RM, Sandhu J, De Ridder D and Stenzl A. Pathophysiology and contributing factors in postprostatectomy incontinence: a review. Eur Urol 2017; 71: 936-944.

[20] Montague DK. Artificial urinary sphincter: long-term results and patient satisfaction. Adv Urol 2012: 2012; 835290.

[21] Tuygun C, Imamoglu A, Keyik B, Alisir I and Yorubulut M. Significance of fibrosis around and/or at external urinary sphincter on pelvic magnetic resonance imaging in patients with post-prostatectomy incontinence. Urology 2006; 68: 1308-1312.

[22] Kadono Y, Ueno S, Iwamoto D, Takezawa Y, Nohara T, Izumi K, Mizokami A and Namiki M. Chronological urodynamic evaluation of changing bladder and urethral functions after robot-assisted radical prostatectomy. Urology 2015; 85: 1441-1447.

[23] Canning A, Raison N, Aydin A, Cheikh Youssef S, Khan S, Dasgupta P and Ahmed K. A systematic review of treatment options for post-prostatectomy incontinence. World J Urol 2022; 40: 2617-2626.

[24] Bauer RM, Bastian PJ, Gozzi C and Stief CG. Postprostatectomy incontinence: all about diagnosis and management. Eur Urol 2009; 55: 322-333.

[25] Castellan P, Ferretti S, Litterio G, Marchioni M and Schips L. Management of urinary incontinence following radical prostatectomy: challenges and solutions. Ther Clin Risk Manag 2023; 19: 43-56.

[26] Ostrowski I, Śledź E, Wilamowski J, Józefczak M, Dyś W, Ciechan J, Drewa T and Chłosta PL. Patients' quality of life after implantation of ZSI 375 artificial urinary sphincter due to stress urinary incontinence. Cent European J Urol 2020; 73: 178-186.

[27] Constable L, Abrams P, Cooper D, Kilonzo M, Cotterill N, Harding C, Drake MJ, Pardoe MN, McDonald A, Smith R, Norrie J, McCormack K, Ramsay C, Uren A, Mundy T, Glazener C and MacLennan G. Synthetic sling or artificial urinary sphincter for men with urodynamic stress incontinence after prostate surgery: the MASTER non-inferiority RCT. Health Technol Assess 2022; 26: 1-152.

[28] Kadono Y, Nohara T, Kawaguchi S, Iwamoto H, Yaegashi H, Shigehara K, Izumi K and Mizokami A. Impact of pelvic anatomical changes caused by radical prostatectomy. Cancers (Basel) 2022; 14: 3050.

[29] Gerullis H, Quast S, Eimer C, Bagner JW and Otto T. Sphincter lesions after radical prostatectomy-evaluation and classification. J Endourol 2011; 25: 1075-1080.

[30] Desautel MG, Kapoor R and Badlani GH. Sphincteric incontinence: the primary cause of post-prostatectomy incontinence in patients with prostate cancer. Neurourol Urodyn 1997; 16: 153-160.

[31] Bessede T, Sooriakumaran P, Takenaka A and Tewari A. Neural supply of the male urethral sphincter: comprehensive anatomical review and implications for continence recovery after radical prostatectomy. World J Urol 2017; 35: 549-565.

[32] Nyarangi-Dix JN, Radtke JP, Hadaschik B, Pahernik S and Hohenfellner M. Impact of complete bladder neck preservation on urinary continence, quality of life and surgical margins after radical prostatectomy: a randomized, controlled, single blind trial. J Urol 2013; 189: 891-898.

[33] Li PC and Ding DC. Stem-cell therapy in stress urinary incontinence: a review. Tzu Chi Med J 2022; 35: 111-119.

[34] Manodoro S, Frigerio M, Barba M, Bosio S, de Vitis LA and Marconi AM. Stem cells in clinical trials for pelvic floor disorders: a systematic literature review. Reprod Sci 2022; 29: 1710-1720.

[35] Liu X, Wang S, Wu S, Hao Q, Li Y, Guo Z and Wang W. Exosomes secreted by adipose-derived mesenchymal stem cells regulate type I collagen metabolism in fibroblasts from women with stress urinary incontinence. Stem Cell Res Ther 2018; 9: 159.

[36] Andersson KE and Williams K. Cellular regenerative therapy in stress urinary incontinence: new frontiers?-a narrative review. Transl Androl Urol 2024; 13: 1709-1716.

[37] Adamowicz J, Kluth LA, Pokrywczynska M and Drewa T. Tissue engineering and its potential to reduce prostate cancer treatment sequelae-narrative review. Front Surg 2021; 8: 644057.

[38] Liu X, Li T, Zhang J, Lin X, Wang W, Fan X and Wang L. Mesenchymal stem cell-based therapy for female stress urinary incontinence. Front Cell Dev Biol 2023; 11: 1007703.

[39] Seval MM and Koyuncu K. Current status of stem cell treatments and innovative approaches for stress urinary incontinence. Front Med (Lausanne) 2022; 9: 1073758.

[40] Rivero Belenchón I, Gómez Rivas J, Medina López RA, Checcucci E, Taratkin M, Puliatti S,

Kowalewski KF, Cacciamani G, Congregado Ruíz CB, Castro C and Enikeev D. New therapies for neurovascular bundles regeneration after radical prostatectomy: a narrative review on clinical studies. Front Urol 2022; 2: 923064.

[41] Garcia-Arranz M, Alonso-Gregorio S, Fontana-Portella P, Bravo E, Diez Sebastian J, Fernandez-Santos ME and Garcia-Olmo D. Two phase I/II clinical trials for the treatment of urinary incontinence with autologous mesenchymal stem cells. Stem Cells Transl Med 2020; 9: 1500-1508.

[42] Wu R, Huang C, Wu Q, Jia X, Liu M, Xue Z, Qiu Y, Niu X and Wang Y. Exosomes secreted by urine-derived stem cells improve stress urinary incontinence by promoting repair of pubococcygeus muscle injury in rats. Stem Cell Res Ther 2019; 10: 80.

[43] Nasrollahzadeh Saravi M, Mohseni M, Menbari Oskouie I, Razavi J, Delgado Cidranes E and Majidi Zolbin M. Exosome therapy in stress urinary incontinence: a comprehensive literature review. Biomedicines 2025; 13: 1229.

[44] Lin G, Wang G, Banie L, Ning H, Shindel AW, Fandel TM, Lue TF and Lin CS. Treatment of stress urinary incontinence with adipose tissue-derived stem cells. Cytotherapy 2010; 12: 88-95.

[45] Carlson K, Andrews M, Bascom A, Baverstock R, Campeau L, Dumoulin C, Labossiere J, Locke J, Nadeau G and Welk B. 2024 Canadian urological association guideline: female stress urinary incontinence. Can Urol Assoc J 2024; 18: 83-102.

[46] Ganzer R, Stolzenburg JU, Neuhaus J, Weber F, Burger M and Bründl J. Is the striated urethral sphincter at risk by standard suture ligation of the dorsal vascular complex in radical prostatectomy? An anatomic study. Urology 2014; 84: 1453-1458.

[47] Yiou R, Mahrouf-Yorgov M, Trébeau C, Zanaty M, Lecointe C, Souktani R, Zadigue P, Figeac F and Rodriguez AM. Delivery of human mesenchymal adipose-derived stem cells restores multiple urological dysfunctions in a rat model mimicking radical prostatectomy damages through tissue-specific paracrine mechanisms. Stem Cells 2016; 34: 392-404.

[48] Ni J, Li H, Zhou Y, Gu B, Xu Y, Fu Q, Peng X, Cao N, Fu Q, Jin M, Sun G, Wang J, Jin Y and Liu F. Therapeutic potential of human adipose-derived stem cell exosomes in stress urinary incontinence - an in vitro and in vivo study. Cell Physiol Biochem 2018; 48: 1710-1722.

[49] Zhang Q, Liu J, Wang W, Lin W, Ahmed W, Duan W, Huang S, Zhu Z and Chen L. The role of exosomes derived from stem cells in nerve regeneration: a contribution to neurological repair. Exp Neurol 2024; 380: 114882.

[50] Gill BC, Sun DZ and Damaser MS. Stem cells for urinary incontinence: functional differentiation or cytokine effects? Urology 2018; 117: 9-17.

[51] Nakano Y, Uchiyama M, Arima T, Nagasaka S, Igarashi T, Shimizu A and Takahashi H. PPARα agonist suppresses inflammation after corneal alkali burn by suppressing proinflammatory cytokines, MCP-1, and Nuclear Translocation of NF-κB. Molecules 2018; 24: 114.

[52] Barakat B, Franke K, Schakaki S, Hijazi S, Hasselhof V and Vögeli TA. Stem cell applications in regenerative medicine for stress urinary incontinence: a review of effectiveness based on clinical trials. Arab J Urol 2020; 18: 194-205.

[53] Wang L, Wang Y, Xiang Y, Ma J, Zhang H, Dai J, Hou Y, Yang Y, Ma J and Li H. An in vitro study on extracellular vesicles from adipose-derived mesenchymal stem cells in protecting stress urinary incontinence through microRNA-93/F3 axis. Front Endocrinol (Lausanne) 2021; 12: 693977.

[54] Knoll J, Amend B, Harland N, Isser S, Bézière N, Kraushaar U, Stenzl A and Aicher WK. Cell therapy by mesenchymal stromal cells versus myoblasts in a pig model of urinary incontinence. Tissue Eng Part A 2024; 30: 14-30.

[55] Okabe YT, Shimizu S, Suetake Y, Matsui-Hirai H, Hasegawa S, Takanari K, Toriyama K, Kamei Y, Yamamoto T, Mizuno M and Gotoh M. Biological characterization of adipose-derived regenerative cells used for the treatment of stress urinary incontinence. Int J Urol 2021; 28: 115-124.

[56] Li GY, Zhou F, Gong YQ, Cui WS, Yuan YM, Song WD, Xin H, Liu T, Li WR, Gao ZZ, Liu J, Guo YL and Xin ZC. Activation of VEGF and ERK1/2 and improvement of urethral function by adipose-derived stem cells in a rat stress urinary incontinence model. Urology 2012; 80: 953, e1-8.

[57] Usas A and Huard J. Muscle-derived stem cells for tissue engineering and regenerative therapy. Biomaterials 2007; 28: 5401-5406.

[58] Nakajima N, Tamaki T, Hirata M, Soeda S, Nitta M, Hoshi A and Terachi T. Purified human skeletal muscle-derived stem cells enhance the repair and regeneration in the damaged urethra. Transplantation 2017; 101: 2312-2320.

[59] Kemp KC, Hows J and Donaldson C. Bone marrow-derived mesenchymal stem cells. Leuk Lymphoma 2005; 46: 1531-1544.

[60] Bhat S, Viswanathan P, Chandanala S, Prasanna SJ and Seetharam RN. Expansion and characterization of bone marrow derived human mesenchymal stromal cells in serum-free conditions. Sci Rep 2021; 11: 3403.

[61] Vasiliadis AV and Galanis N. Human bone marrow-derived mesenchymal stem cells from dif-

ferent bone sources: a panorama. Stem Cell Investig 2020; 7: 15.

[62] Takahashi K and Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006; 126: 663-676.

[63] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K and Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131: 861-872.

[64] de Lázaro I, Yilmazer A and Kostarelos K. Induced pluripotent stem (iPS) cells: a new source for cell-based therapeutics? J Control Release 2014; 185: 37-44.

[65] Aboul-Soud MAM, Alzahrani AJ and Mahmoud A. Induced pluripotent stem cells (iPSCs)-roles in regenerative therapies, disease modelling and drug screening. Cells 2021; 10: 2319.

[66] Yin X, Li Q, Shu Y, Wang H, Thomas B, Maxwell JT and Zhang Y. Exploiting urine-derived induced pluripotent stem cells for advancing precision medicine in cell therapy, disease modeling, and drug testing. J Biomed Sci 2024; 31: 47.

[67] Zhang Y, McNeill E, Tian H, Soker S, Andersson KE, Yoo JJ and Atala A. Urine derived cells are a potential source for urological tissue reconstruction. J Urol 2008; 180: 2226-2233.

[68] Raffo G, Sappia D, Dominici D, Rozenbaum M, García J, Lavigne M and Correa M. Endoscopic implantation of autologous myoblasts for stress urinary incontinence and evaluation of its efficacy in sphincterotomized rabbits. Actas Urol Esp (Engl Ed) 2023; 47: 588-597.

[69] Imamura T, Ishizuka O and Nishizawa O. Autologous bone marrow-derived cells regenerate urethral sphincters. Low Urin Tract Symptoms 2012; 4 Suppl 1: 87-94.

[70] Vaegler M, Lenis AT, Daum L, Amend B, Stenzl A, Toomey P, Renninger M, Damaser MS and Sievert KD. Stem cell therapy for voiding and erectile dysfunction. Nat Rev Urol 2012; 9: 435-447.

[71] Castiglione F, Dewulf K, Hakim L, Weyne E, Montorsi F, Russo A, Boeri L, Bivalacqua TJ, De Ridder D, Joniau S, Albersen M and Hedlund P. Adipose-derived stem cells counteract urethral stricture formation in rats. Eur Urol 2016; 70: 1032-1041.

[72] Tran C and Damaser MS. The potential role of stem cells in the treatment of urinary incontinence. Ther Adv Urol 2015; 7: 22-40.

[73] Kishimoto S, Ishizuka M, Inoue KI, Yamanishi T, Shimizu T, Kaga K, Aoki T and Kubota K. Local transplantation of syngeneic adipose stromal vascular fraction ameliorates damaged anal sphincter function in a rat model of vaginal distension. Surgery 2022; 172: 1093-1101.

[74] Turco MP, de Souza AB, de Campos Sousa I, Fratini P, Veras MM, Rodrigues MN, de Bessa J Jr, Brolio MP, Leite KRM, Bruschini H, Srougi M, Miglino MA and Gomes CM. Periurethral muscle-derived mononuclear cell injection improves urethral sphincter restoration in rats. Neurourol Urodyn 2017; 36: 2011-2018.

[75] Yang H, Chen B, Deng J, Zhuang G, Wu S, Liu G, Deng C, Yang G, Qiu X, Wei P, Wang X and Zhang Y. Characterization of rabbit urine-derived stem cells for potential application in lower urinary tract tissue regeneration. Cell Tissue Res 2018; 374: 303-315.

[76] Kim BS, Chun SY, Lee JK, Lim HJ, Bae JS, Chung HY, Atala A, Soker S, Yoo JJ and Kwon TG. Human amniotic fluid stem cell injection therapy for urethral sphincter regeneration in an animal model. BMC Med 2012; 10: 94.

[77] Naji M, Ansari E, Besharati S, Hajiabbas M, Mohammadi Torbati P, Asghari Vostikolaee MH, Hajinasrollah M and Sharifiaghdas F. Tissue-engineered sub-urethral sling with muscle-derived cells for urethral sphincter regeneration in an animal model of stress urinary incontinence. Urologia 2024; 91: 834-841.

[78] Cannon TW, Lee JY, Somogyi G, Pruchnic R, Smith CP, Huard J and Chancellor MB. Improved sphincter contractility after allogenic muscle-derived progenitor cell injection into the denervated rat urethra. Urology 2003; 62: 958-963.

[79] Lim JJ, Jang JB, Kim JY, Moon SH, Lee CN and Lee KJ. Human umbilical cord blood mononuclear cell transplantation in rats with intrinsic sphincter deficiency. J Korean Med Sci 2010; 25: 663-670.

[80] Corcos J, Loutochin O, Campeau L, Eliopoulos N, Bouchentouf M, Blok B and Galipeau J. Bone marrow mesenchymal stromal cell therapy for external urethral sphincter restoration in a rat model of stress urinary incontinence. Neurourol Urodyn 2011; 30: 447-455.

[81] Eberli D, Aboushwareb T, Soker S, Yoo JJ and Atala A. Muscle precursor cells for the restoration of irreversibly damaged sphincter function. Cell Transplant 2012; 21: 2089-98.

[82] Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, Lund L and Sheikh SP. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. EBioMedicine 2016; 5: 204-210.

[83] Choi JY, Kim TH, Yang JD, Suh JS and Kwon TG. Adipose-derived regenerative cell injection therapy for postprostatectomy incontinence: a phase I clinical study. Yonsei Med J 2016; 57: 1152-1158.

[84] Albu S, Kumru H, Coll R, Vives J, Vallés M, Benito-Penalva J, Rodríguez L, Codinach M, Hernández J, Navarro X and Vidal J. Clinical effects of intrathecal administration of expanded Wharton jelly mesenchymal stromal cells in patients with chronic complete spinal cord injury: a randomized controlled study. Cytotherapy 2021; 23: 146-156.

[85] Akhlaghpasand M, Tavanaei R, Allameh F, Hosseinpoor M, Toreyhi H, Golmohammadi M, Hajarizadeh A, Alikhani A, Hafizi M, Oraee-Yazdani M, Zali A and Oraee-Yazdani S. Improvement of neurogenic bladder dysfunction following combined cell therapy with mesenchymal stem cell and schwann cell in spinal cord injury: a randomized, open-label, phase II clinical trial. World Neurosurg 2025; 194: 123402.

[86] Chermansky C, Mitsogiannis I, Abrams P and Apostolidis A. Stem cells and lower urinary tract dysfunction: has its potential finally reached clinical maturity? ICI-RS2018. Neurourol Urodyn 2019; 38 Suppl 5: S134-S141.

[87] Bosholm CC, Zhu H, Yu P, Cheng K, Murphy SV, McNutt PM and Zhang Y. Therapeutic benefits of stem cells and exosomes for sulfur-mustard-induced tissue damage. Int J Mol Sci 2023; 24: 9947.

[88] Gotoh M, Yamamoto T, Shimizu S, Matsukawa Y, Kato M, Majima T, Takai S, Funahashi Y and Toriyama K. Treatment of male stress urinary incontinence using autologous adipose-derived regenerative cells: long-term efficacy and safety. Int J Urol 2019; 26: 400-405.

[89] Gotoh M, Yamamoto T, Kato M, Majima T, Toriyama K, Kamei Y, Matsukawa Y, Hirakawa A and Funahashi Y. Regenerative treatment of male stress urinary incontinence by periurethral injection of autologous adipose-derived regenerative cells: 1-year outcomes in 11 patients. Int J Urol 2014; 21: 294-300.

[90] Yamamoto T, Gotoh M, Kato M, Majima T, Toriyama K, Kamei Y, Iwaguro H, Matsukawa Y and Funahashi Y. Periurethral injection of autologous adipose-derived regenerative cells for the treatment of male stress urinary incontinence: report of three initial cases. Int J Urol 2012; 19: 652-659.

[91] Yamamoto T, Gotoh M, Hattori R, Toriyama K, Kamei Y, Iwaguro H, Matsukawa Y and Funahashi Y. Periurethral injection of autologous adipose-derived stem cells for the treatment of stress urinary incontinence in patients undergoing radical prostatectomy: report of two initial cases. Int J Urol 2010; 17: 75-82.

[92] Zhang H, Huang J, Liu J, Li Y and Gao Y. BMMSC-sEV-derived miR-328a-3p promotes ECM remodeling of damaged urethral sphincters via the Sirt7/TGFβ signaling pathway. Stem Cell Res Ther 2020; 11: 286.

[93] Abdulmalek OAAY, Husain KH, AlKhalifa HKAA, Alturani MMAB, Butler AE and Moin ASM. Therapeutic applications of stem cell-derived exosomes. Int J Mol Sci 2024; 25: 3562.

[94] Liang X, Zhang L, Wang S, Han Q and Zhao RC. Exosomes secreted by mesenchymal stem cells promote endothelial cell angiogenesis by transferring miR-125a. J Cell Sci 2016; 129: 2182-2189.

[95] Salehpour A, Karimi Z, Ghasemi Zadeh M, Afshar M, Kameli A, Mooseli F, Zare M and Afshar A. Therapeutic potential of mesenchymal stem cell-derived exosomes and miRNAs in neuronal regeneration and rejuvenation in neurological disorders: a mini review. Front Cell Neurosci 2024; 18: 1427525.

[96] Rolland TJ, Peterson TE, Singh RD, Rizzo SA, Boroumand S, Shi A, Witt TA, Nagel M, Kisby CK, Park S, Rowe LA, Paradise CR, Becher LRE, Paradise BD, Stalboerger PG, Trabuco EC and Behfar A. Exosome biopotentiated hydrogel restores damaged skeletal muscle in a porcine model of stress urinary incontinence. NPJ Regen Med 2022; 7: 58.

[97] Liu C, Li Q, Ma JX, Lu B, Criswell T and Zhang Y. Exosome-mediated renal protection: halting the progression of fibrosis. Genes Dis 2023; 11: 101117.

[98] Sun T, Li M, Liu Q, Yu A, Cheng K, Ma J, Murphy S, McNutt PM and Zhang Y. Insights into optimizing exosome therapies for acute skin wound healing and other tissue repair. Front Med 2024; 18: 258-284.

[99] Deng C, Xie Y, Zhang C, Ouyang B, Chen H, Lv L, Yao J, Liang X, Zhang Y, Sun X, Deng C and Liu G. Urine-derived stem cells facilitate endogenous spermatogenesis restoration of busulfan-induced nonobstructive azoospermic mice by paracrine exosomes. Stem Cells Dev 2019; 28: 1322-1333.

[100] Tourinho-Barbosa R, Srougi V, Nunes-Silva I, Baghdadi M, Rembeyo G, Eiffel SS, Barret E, Rozet F, Galiano M, Cathelineau X and Sanchez-Salas R. Biochemical recurrence after radical prostatectomy: what does it mean? Int Braz J Urol 2018; 44: 14-21.

[101] Kupelian PA, Buchsbaum JC, Elshaikh M, Reddy CA, Zippe C and Klein EA. Factors affecting recurrence rates after prostatectomy or radiotherapy in localized prostate carcinoma patients with biopsy Gleason score 8 or above. Cancer 2002; 95: 2302-2307.

[102] Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC and Partin AW. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005; 294: 433-439.

[103] Maqsood M, Kang M, Wu X, Chen J, Teng L and Qiu L. Adult mesenchymal stem cells and their

exosomes: sources, characteristics, and application in regenerative medicine. Life Sci 2020; 256: 118002.

[104] Ma CY, Zhai Y, Li CT, Liu J, Xu X, Chen H, Tse HF and Lian Q. Translating mesenchymal stem cell and their exosome research into GMP compliant advanced therapy products: promises, problems and prospects. Med Res Rev 2024; 44: 919-938.

[105] Zhang J, Tian X, Li Y, Fang C, Yang F, Dong L, Shen Y, Pu S, Li J, Chang D, Lei L and Yu X. Stem cell-derived exosomes: a comprehensive review of biomedical applications, challenges, and future directions. Int J Nanomedicine 2025; 20: 10857-10905.

[106] Chung E. Stem-cell-based therapy in the field of urology: a review of stem cell basic science, clinical applications and future directions in the treatment of various sexual and urinary conditions. Expert Opin Biol Ther 2015; 15: 1623-1632.

[107] Pan W, Chen H, Wang A, Wang F and Zhang X. Challenges and strategies: scalable and efficient production of mesenchymal stem cells-derived exosomes for cell-free therapy. Life Sci 2023; 319: 121524.

[108] Wang Z. Assessing tumorigenicity in stem cell-derived therapeutic products: a critical step in safeguarding regenerative medicine. Bioengineering (Basel) 2023; 10: 857.

[109] Abbasi-Malati Z, Azizi SG, Milani SZ, Serej ZA, Mardi N, Amiri Z, Sanaat Z and Rahbarghazi R. Tumorigenic and tumoricidal properties of exosomes in cancers; a forward look. Cell Commun Signal 2024; 22: 130.

[110] Jafari D, Shajari S, Jafari R, Mardi N, Gomari H, Ganji F, Forouzandeh Moghadam M and Samadikuchaksaraei A. Designer exosomes: a new platform for biotechnology therapeutics. BioDrugs 2020; 34: 567-586.

[111] Marote A, Teixeira FG, Mendes-Pinheiro B and Salgado AJ. MSCs-derived exosomes: cell-secreted nanovesicles with regenerative potential. Front Pharmacol 2016; 7: 231.