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**Regenerative medicine based applications to combat stress urinary incontinence**

Thaker H *et al*. Tissue engineering for stress urinary incontinence

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**Abstract**

Stress urinary incontinence (SUI), as an isolated symptom, is not a life threatening condition. However, the fear of unexpected urine leakage contributes to a significant decline in quality of life parameters for afflicted patients. Compared to other forms of incontinence, SUI cannot be easily treated with pharmacotherapy since it is inherently an anatomic problem. Treatment options include the use of bio-injectable materials to enhance closing pressures, and the placement of slings to bolster fascial support to the urethra. However, histologic findings of degeneration in the incontinent urethral sphincter invite the use of tissues engineering strategies to regenerate structures that aid in promoting continence. In this review, we will assess the role of stem cells in restoring multiple anatomic and physiological aspects of the sphincter. In particular, mesenchymal stem cells and CD34+ cells have shown great promise to differentiate into muscular and vascular components, respectively. Evidence supporting the use of cytokines and growth factors such as hypoxia-inducible factor 1-alpha, vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor and insulin-like growth factor further enhance the viability and direction of differentiation. Bridging the benefits of stem cells and growth factors involves the use of synthetic scaffolds like poly (1,8-octanediol-co-citrate) (POC) thin films. POC scaffolds are synthetic, elastomeric polymers that serve as substrates for cell growth, and upon degradation, release growth factors to the microenvironment in a controlled, predictable fashion. The combination of cellular, cytokine and scaffold elements aims to address the pathologic deficits to urinary incontinence, with a goal to improve patient symptoms and overall quality of life.

**Key words:** Stress urinary incontinence; Smooth muscle; Tissue engineering; Regeneration; Stem cells; Biomaterials; Angiogenesis; Sphincter

**Core tip:** Stress urinary incontinence is a condition which affects millions of women on a world-wide basis. Current surgical strategies to alleviate the symptoms involved with this condition are temporary stop-gap measures. With the advent of tissue engineering strategies in combination with stem cells, the reality of creating a functional replacement for anatomic structures involved in stress urinary incontinence can be a reality.

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**INTRODUCTION**

Symptoms of the lower urinary tract in women, such as urinary incontinence, account for a significant number of outpatient consultations to urogynecologists[1]. Several risk factors have been identified to explain the onset and persistence of this condition, particularly since the prevalence of urinary incontinence among adult women is approximately 16%-30%[2,3]. The occurrence of urinary incontinence is closely correlated with rising age[4], along with obesity through increased pressure on the pelvic floor, diabetes mellitus causing microvascular and neuropathic changes, and prior pelvic surgeries for the fascial, muscular and nerve stress it imparts. Among younger women, pregnancy and subsequent vaginal delivery leads to post-partum incontinence in up to 28% of the population. Bladder outlet compression, pelvic floor strain that elongates the pudendal nerve, and a prolonged second stage of labor all contribute towards urinary leakage[5-7]. Less often, patients with a chronic cough or those with fascial weakness secondary to a defect in collagen metabolism may have incontinence as well[8]. In adult men, direct injury to the neurovascular bundle and fascial planes during radical prostatectomy is a leading cause of incontinence[9].

A Scandinavian study reports that as many as 64% of women with urinary incontinence issues do not consult their primary care physician for a diagnostic work up of their symptoms[10]. A similar study in the US observed a rate of about 45%[11]. The prevalence of urinary incontinence, therefore, could be much higher than documented. Though not life-threatening, patients endure a dramatic decline to their quality of life. A survey across Europe and the US documented this subjective aspect, showing that confidence, self-perception, levels of physical activity and social engagement were negatively impacted by incontinence[12-14]. Not surprisingly, reports show a higher prevalence of anxiety and depression among these patients as well[15,16]. For the elderly in nursing homes, uncontrollable passage of urine irritates the perineal skin, causing dermatitis and discomfort that is difficult to alleviate[17].

Urinary incontinence is a condition in which there is involuntary leakage of urine that can be attributed to a number of differing factors. Depending on the presentation and history, incontinence is divided into several groups. Stress urinary incontinence (SUI) is an involuntary loss of urine that occurs with increased abdominal exertion, exemplified during coughing, sneezing, laughing or lifting. If the bladder is retaining urine in excessive amounts, small increases to abdominal pressure will produce an unwanted leak. Yet this symptom can still occur within the normal range of bladder fullness, such as in defects to the urethra or the intrinsic sphincter in retaining urine. A laxity of supportive structures to the pelvic floor and bladder means that increased pressures cannot be counteracted. Urge urinary incontinence presents with frequency causing low volume output, urgency, and nocturia. The leakage of urine is typically accompanied by or preceded by a sense of urgency. A combination of these two types is described as mixed urinary incontinence, where increased abdominal pressures cause urinary leakage and concomitant urgency. Overactive bladder is characterized by urgency, with or without incontinence. Less common voiding abnormalities include conditions such as nocturnal enuresis and continuous urinary incontinence. An acute onset of urinary incontinence may suggest an underlying neurologic degenerative disease or malignancy, and should therefore be considered in the differential diagnosis[18-20].

Though the development of urinary incontinence is multifactorial in nature[21], all variations of disease in SUI ultimately manifest as either urethral hypermobility or urethral sphincter dysfunction. The effects of aging are particularly well described to demonstrate this. Increasing age leads to urethral musculature degeneration and neurologic injury[22]. The number of striated muscle fibers diminishes with histologic thinning noted at the proximal vesicle neck (supported by the U-shaped detrusor) and at the dorsal wall of the urethra (encircled by striated sphincter muscles). In addition, an age-related weakening of the endopelvic fascia reduces the support to the urethra, causing an inability to maintain the physiologic 90-120 degree vesicourethral angle required to maintain continence[23]. What results is termed urethral hypermobility. The endopelvic fascial layer is a dense, fibrous connective tissue layer surrounding the vagina, with attachments to the arcus tendinous fascia, the pubic bone ventrally, and the ischial spine dorsally[23]. Degenerative changes diminish the ability of the urethra to generate pressure against stress. As an example, a staccato cough creates a 150 cm H2O increase in abdominal pressure, which the urethra must counteract during non-micturation times. A more compliant fascial layer threatens to lose continence during such transient pressures changes.

Initiating therapy for SUI requires the identification and understanding of the functional components comprising the urinary sphincter. The nerve supply to the lower urinary tract consists of three important innervations (Figure 1). First, pelvic nerves (S2-S4) provide parasympathetic innervations to the detrusor muscle and urethral smooth muscle sphincter. As an excitatory motor efferent nerve, the pelvic nerves initiate and coordinate micturition by contracting the detrusor and relaxing the sphincter. Second, hypograstric nerves (T2-L3) are sympathetic innervations to the trigone, bladder neck internal sphincter and detrusor muscle. These nerves allow for urinary retention, and inhibit detrusor activity. Lastly, the pudendal nerves (S2-S4) of the sacral plexus innervate the external urethral sphincter (EUS) and striated muscles of the pelvic floor. The EUS consists of circular striated “slow twitch” fibers that sustain long periods of contraction, and pelvic basin muscles like the pubococcygeus contains slow and fast twitch fibers for reflex contraction during a cough or sneeze. The pudendal nerve arises from Onuf’s nucleus, traverses Alcock’s canal and enters the ischiorectal fossa to innervate the EUS[6]. This trajectory places the nerve between the sacrospinous and sacrotuberous ligaments, which makes it vulnerable to compression and injury.

**MEDICAL AND SURGICAL MANAGEMENT OF SUI**

Conservative management of SUI involves lifestyle and behavioral changes, weight loss[24], bladder training[25], Kegel exercises to strengthen the pelvic floor and pharmacotherapy to improve urethral muscle tone[26-28]. Unlike other forms of urinary incontinence, there is a dearth of pharmacologic options that are effective for SUI. Alpha-adrenergic receptors at the bladder neck and urethra can be targeted with pseudoepherine and ephedrine to stimulate smooth muscle contraction[27,29]. Though this use may theoretically be suited to improve symptoms, the cardiovascular side effect profile precludes many patients from this therapy[30]. Imipramine, a tricyclic antidepressant with strong anti-cholinergic effects, also promotes urethral sphincter closure and urinary retention. This drug, however, poses a significant risk of orthostatic hypotension, which is often contraindicated in the elderly population. Lately, the use of duloxetine outside of the US has shown some promise, though the mechanism of action hardly addresses the underlying cause[31,32]. Patients with SUI and concomitant urge symptoms have more therapeutic options, including anti-muscarinic agents and oxybutynin[33].

Despite these initial efforts to gain continence, most of these patients are refractory to treatment and are invariably referred for surgical intervention. The goals of surgery are to reduce the number of episodes of incontinence each day or to reduce the volume of leaked urine, with the ultimate aim of achieving complete continence. Surgery can either support the compression of the urethra, or augment coaptation to create a better seal. Pre-operative assessment of surgical candidates begins with a detailed a history with bladder diary recordings, and a physical, including a bimanual exam. A urinalysis to rule out infectious causes is indicated, followed by a cough stress test. In this test, the clinician visualizes the leakage of urine from a full bladder while the patient coughs. The volume of urine leak, collected on chux padding, may signify the degree of stress incontinence. Once the diagnosis of SUI is confirmed, most patients move on to urodynamic testing.

Urodynamic testing is expensive and subject to operator variability[34,35], but it provides two important measurements for the management of SUI. The first is leak point pressure (LPP). LPP measures the intravesical pressure at which urine leakage occurs when the patient is asked to strain or subjected to the Valsalva manuever. The patient must be careful to not induce a detrusor contraction. This is a measurement of intrinsic sphincter deficiency, and a LPP less than 60 cm H2O is suggestive of SUI. The second measurement is the maximum urethral pressure generated, which is part of the urethral pressure profile. Profilometry also documents maximum urethral closure pressure, functional urethral length and the pressure transmission ratio. Maximum urethral pressures less than 20-30 mmHg are suggestive of SUI, and warrants the use of sling placement or periurethral bulking agent injections[36].

The surgical approach to SUI involves either placement of slings to support of the urethra, or injection of biomaterials to increase urethral coaptation. Minimally invasive sling placement is currently the most common intervention for SUI[37]. Through a vaginal incision, a thin mesh of polypropylene thread material is positioned at the midurethra or at the bladder neck[38]. The sling behaves like an immobile floor, onto which the urethra can contract[39]. This strategy assumes the incontinent sphincter is indeed caused by urethral hypermobility, so supporting the plane of contraction would limit the angulation. Midurethral slings may be placed with either a retropubic or transobturator approach. A multicenter, randomized trial shows equivalent outcomes regardless of approach [40], though some studies still report better outcomes with a tension-free vaginal tape retropubic sling[41]. Newer interventions using a single incision sling or an adjustable sling have also shown promise[42].

Midurethral sling procedures have largely replaced the older Marshall-Marchetti-Krantz and Burch techniques of colposuspension[38,43]. Though these procedures have success rates of up to 88%[44], complications of urinary retention, de novo urgency, posterior vaginal wall prolapse, and osteitis pubis have been documented [45]. In contrast, a Cochrane review of sling surgeries showed that the minimally invasive approach lessens operative times and decreases post-operative voiding dysfunction[38].

Sling materials have traditionally been sourced from autologous rectus fascia, fascia lata or small intestinal submucosa (SIS)[46-48]. Cadaveric allografts from the dura, dermis or fascia lata have been shown to be inferior to autologous grafts in the long term based on the frequency of recurrent incontinence[49]. However, harvesting autologous fascial layers requires longer operative times, longer recovery times and more pain for the patient [50], despite evidence suggesting they are equivalent to synthetic slings[51]. For this reason, synthetic materials have become the mainstay in slings.

Sling placement, albeit a minimally invasive procedure, is not without risks and complications. Establishing an appropriate tension across the urethra is challenging, and can result in urinary retention or failure to alleviate symptoms. Both outcomes require release and adjustment of the sling, which is another surgical procedure. Other risks include bladder or urethral laceration, perforation and urinary tract infections (UTI)[52]. Occasionally, these issues are secondary to erosion of the mesh through soft tissue. These patients suffer from vaginal discharge, post-coital spotting, dyspareunia, and frequent UTIs. Despite these potential complications, the majority of patients do achieve freedom from incontinence, and self-reported improvements to sexual activity[53,54], and reductions in coital incontinence[55].

Injecting biomaterials to augment the urethral mucosa has become an alternative to urethral slings. Bulking agents have the greatest benefit for intrinsic sphincter defects with a LPP of less than 60 cm H2O. Regardless of where the injection is placed, studies have shown equivalent success with biomaterials in the periurethral, transurethral, midurethral and proximal neck areas[56,57]. The differences then lie in the biomaterial composition.

**APPLICATIONS OF TISSUE ENGINEERING TO SUI**

***Tissue engineering the urethral sling***

Current surgical standards use non-antigenic synthetic materials for slings. Over the past few years, studies have investigated the potential role of stem cells in SUI treatment. In a study by Zou *et al*[58], acellular silk slings were tested against slings seeded with autologous bone marrow derived mesenchymal stem cells (MSCs) on rats with bilateral sciatic nerve transection. MSCs were isolated from bone marrow aspirates using flow cytometry against CD34, CD44 and CD105 cell surface epitopes. Sciatic nerve transection, among other methods, is a means to produce genuine SUI pathology[59]. At 12 wk post-implantation, MSC/silk slings had double the collagen fiber formation of silk slings alone, evidenced by a higher Young’s modulus (4.468 *±* 0.510 MPa) and higher failure force (2.436 *±* 0.192 *n*) as compared to silk slings alone. The mean Young’s modulus of silk slings alone was 3.045 *±* 0.388 MPa, with a failure force of 1.521 *±* 0.087 *n*. The collagen formation improved sling integration with the native urethral tissue. However, both MSCs/silk and silk alone constructs performed equally in increasing the LPP (MSCs/silk at 36.3 *±* 3.1 cm H2O *vs* silk alone at 38.0 *±* 3.3 cm H2O). Nonetheless, this study demonstrates that the introduction of MSCs into the urethral environment does not cause any significant inflammation, scarring or adverse effects. Other scaffolds may be better suited in lieu of silk. It is important to note that even though a stem cell seeded construct could improve integration of slings into the urethra, the operative risks remain the same as that for current sling placements. Additionally, there is no evidence demonstrating that cellular slings have a decreased risk of mesh erosion over commercially available slings.

***Tissue engineering the urethral sphincter***

Attribution of SUI to intrinsic sphincter degeneration poses a challenging problem from a therapeutic standpoint. Sphincter degeneration involves the loss of multiple functional tissue types. Efforts to recreate the function of urethral sphincters are best demonstrated through artificial fluid-filled cuffs encircling the urethra. Artificial urinary sphincters have three components: a cuff of 4.5 cm in size, a reservoir with 61-70 cm H2O to mimic urethral pressures, and a pump to permit inflation and deflation controlled by the patient. Sphincters are most commonly placed at the bulbar urethra in men who suffer from post-prostatectomy SUI[9]. Though theoretically purposeful, artificial sphincters are associated with a multitude of complications. Acutely, urethral edema produces pain and discomfort for the patient. Chronically, patients experience atrophy and erosion of the sphincter resulting in irritative voiding symptoms, perineal pain and hematuria[60]. There are presently no controlled trials showing an improvement to symptoms using an artificial device over conventional therapy[61]. As such, we consider the employment of stem cells and tissue engineering techniques to reconstruct the urethral sphincter.

Several studies have established a foundation of infusing stem cells directly into the urethral sphincter. Preparations of MSCs, autologous progenitor muscle cells[62], adipose cells[63], processed lipoaspirate[64,65], human amniotic stem cells[66] and fibroblasts[67] have all been used with variable results[62,68,69] to bolster smooth muscle regeneration and to improve LPPs and urethral closure pressures (Table 1). Few studies have assessed the role of stem cells for the subset of male patients with SUI from prostate-related surgery. In one study, transurethral injections of autologous muscle derived fibroblasts and myoblasts produced complete continence in 65% of the 63 participants, quantified by a pre-operative LPP of 46.3 ± 17.1 cm H2O, and a post-operative LPP of 68.2 ± 24.3 cm H2O[70]. Another study using a similar approach reported improvements to merely 12% of 222 male patients, with no improvements in 46%[71]. While both studies showed that stem cell implantation is a safe procedure in eligible patients, the results do not show a clear benefit as seen in trials with women and SUI.

Using MSCs seems to show the greatest promise, as MSCs have displayed the potential to regenerate both muscle and ganglion components in the sphincter. Corcos *et al* demonstrated in an animal model that injecting BMSCs into denervated urethral sphincters improved LPPs to almost normal, non-SUI levels. This result is argued to be due to the differentiation of MSCs into striated muscle within the urethral microenvironment[72]. Though this evidence is merely histologic, and not in an improvement to symptoms for patients, the concept of creating a functional contractile tissue in the sphincter is worthy of further development.

Mesenchymal stem cell (MSC) use in tissue engineering has become a prominent strategy in a multitude of fields, including urogynecology[73-79]. MSCs express cell surface markers CD29, CD44, CD105, CD166, and are negative for hematopoietic markers such as CD14, CD34, CD40 and CD45[80]. MSCs are also negative for leukocyte common antigen CD45, suggesting that these stem cells escape lymphocyte detection, and thus avoid immune rejection[81,82]. Sourced from the bone marrow, MSCs can be easily isolated from other hematopoietic cells through flow cytometry. MSCs have the capacity to divide 24-40 times *in vitro*, allowing for multiple passages of expansion without losing their multipotent properties or differentiating spontaneously[83]. This advantage, described by Pittenger *et al*[84], permits the differentiation of MSCs by external forces, such as the microenvironment of target tissue itself. Coupled to this environment, MSCs display an immunomodulatory effect[85] that includes the secretion of cytokines to initiate and support tissue regeneration[86]. For these reasons, MSCs must, by minimal criteria, differentiate into osteoblasts, chondrocytes and adipocytes. Yet, the plasticity inherent in MSCs has pushed researchers to generate neural, cardiac, muscular, and other soft tissue lineages. In the realm of urinary tract healing, MSCs are considered a prime candidate since their presence has great therapeutic potential with minimal complications[87,88].

Some centers are already offering stem cell injections into the urethra for patients[89-91]. However, it is unclear whether these cells serve a functional purpose in regenerating damaged sphincters, or whether the cells are merely a bulking agent not unlike injectable biomaterials. In addition, it is recognized that inflammation at the implant site diminishes the ability of injected cells to survive long enough to participate in regeneration[92]. If growth were not sustained over a 7-10 d period, the applications of MSCs would be significantly stunted. Providing a means to enhance cell viability *in vivo* could be achieved by introducing synthetic scaffolds and growth factors.

The harmony of using scaffolds, stem cells and growth factors together has shown promise in a number of tissue engineering projects. Zhao *et al*[93] harvested adipose derived stem cells (ADSCs) and seeded them onto poly(lactic-co-glycolic acid) (PLGA) microparticles containing nerve growth factor (NGF). As a synthetic scaffold, PLGA has been shown to be safe in the urinary tract[94,95]. With periurethral injection into mice, this combination improved the LPP to 22.5 *±* 6.1 cm H2O over treatments lacking either the PLGA or NGF. This result was explained by NGF prolonging the survival of ADSCs, enhancing the urethral muscle area on histology, and increased the density of neurofilaments supporting the sphincter lamina propria. This is the first iconic study where tissue engineering directly addresses the pathology underlying intrinsic sphincter defects. We propose a similar approach, where scaffolds and MSCs are injected not into the periurethral space, but directly into the urethral sphincter.

***Poly(1,8 octanediol-co-citrate) scaffolds to support urethral sphincter regeneration***

The number and variety of polymers synthesized for tissue engineering is rapidly expanding. A popular selection for research is PLGA[96], possessing elastic properties that adapt well to dynamic soft tissue structures. A similar material, poly(1,8-octanediol-co-citrate) (POC), is used by our group for urologic tissue engineering efforts. First established by Ameer *et al*[97], POC thin film (POCf) scaffolds are a highly reproducible elastomeric material[98]. The POCf allows for cell growth, cell infiltration, and for unimpaired exchange of oxygen and nutrient delivery. During polymerization of the scaffold, several aspects of construction can be customized to mimic the compliance, elasticity, and tensile strength measured through Young’s modulus. Equimolar amounts of citric acid and 1,8-octanediol are combined, melted and cooled to make a pre-polymer, and parameters such as temperature and time can be adjusted. Higher temperatures with short polymerization times produce dense films, while low temperatures and long polymerization times yield scaffolds that are less cross-linked. With these modifiable ester-bonding schemes, highly adaptable, labile and reproducible scaffolds can be created specifically for urinary tract tissue targets. Tailoring these parameters also reflects the degradation scheme of POCf, which degrades to nontoxic byproducts of CO2 and H2O *via* non-enzymatic hydrolysis.

Another feature of POC scaffolds, besides providing a highly conducive substrate for cell growth and proliferation, is the ability to deliver growth factors through a controlled release upon scaffold degradation[99]. During the polymerization of POC, small peptides including growth factors and cytokines may be chemically coupled to the scaffold and released upon surface erosion. POCf scaffolds modified with heparan sulfate to hold vascular endothelial growth factor (VEGF), fibroblast growth factor 2 and insulin-like growth factor were studied by Sharma *et al*[99] in a rat model. Heparan sulfate, a highly sulfated glycosaminoglycan, protects bound growth factors to prevent enzymatic degradation. Delivery of the pro-angiogenic growth factors upon break down of the scaffold led to increased vascular growth *in vivo* as compared to controls. The difference in results demonstrates that using POCf for a protracted but focused delivery of growth factors improves tissue healing.

The versatility of POCfs used in consonance with MSCs and growth factors offers the basis to potentially correct for sphincter deficiencies. For pregnancy related SUI, one pathway has been identified to be upregulated in response to vaginal distention and subsequent tissue damage[100]. The pathway involves hypoxia inducible factor-1α, a transcription factor stabilized in hypoxic conditions to induce expression of VEGF. This marker of tissue injury, and the resulting drive for angiogenesis, could potentially home stem cells to the site of injury. Studies by Dissaranan *et al*[101] have shown that pelvic injury *via* vaginal distension is a sufficient nidus for MSC homing to the urethra and levator ani. This phenomenon is speculated to be through chemokine ligand-7. Adding these chemokines to the POC delivery system could therefore boost the response of MSCs in tissue regeneration, and recruit circulating progenitors as well[102,103]. Progenitors stationed in the tissue, such as intrinsic satellite cells, may also be recruited to striated muscle reconstruction[104]. Direct and strong evidence exists that VEGF promotes the growth of myoblasts and increases capillary growth to the regenerating tissue. Interestingly, VEGF was capable of advancing the growth of myoblasts sourced even from older mice, where cells have less capacity to proliferate into functional tissue[105]. Growth factors like basic fibroblast growth factor (bFGF), hepatocyte growth factor and insulin-like growth factor have also contributed to muscle regeneration[106]. Characterization studies have also outlined a multitude of paracrine factors secreted by MSCs that are anti-apoptotic, immunomodulatory, anti-fibrotic, and pro-angiogenic[107]. As previously confirmed, VEGF from MSCs, along with IL-6, MCP-1 and extracellular matrix components, assist in supporting angiogenesis, laying down extracellular matrix, and preventing apoptosis secondary to hypoxia[108].

The significance of bioactive compounds in regeneration was further strengthened by Choi *et al*[109]. In this study, plasmid DNA encoding bFGF was injected into rat periurethral submucosa *via* a PLGA synthetic delivery system. Results indicated that the levels of SM α-actin were elevated due to the bFGF, corresponding to a proliferation of tightly packed smooth muscle. Furthermore, contraction studies, conducted through electrical stimulation, showed a marked elevation in contractile properties for pDNA transfected urethras. Normal, continent urethras generated a contraction force of 36.4 *±* 2.5 tension/mg of tissue, which is not dramatically different from the measured 32.3 *±* 1.5 tension/mg tissue generated in pDNA/PLGA treated incontinent mice.

Three important concepts come out of this study: (1) that a sustained release of pDNA expressing bFGF through PLGA proved beneficial to regeneration; (2) the use of pDNA ensures that regeneration continues beyond the half-life and denaturation of biogenic compounds; and (3) since neither MSCs nor any other cell lines were not utilized in the injection, the improvement to symptoms can be specifically attributed to bFGF.

Integrating POCfs with MSCs and cytokines addresses the muscular aspect of sphincter regeneration. But a more comprehensive approach pays attention to the vascular and neural components as well. Seeding POC with progenitor cells from the bone marrow alongside MSCs could complete these components. Recent insights into CD34+ hematopoietic stem cells (HSCs), harvested from the same bone marrow origin as MSCs, points to a promising adjunct to MSCS. HSCs express von Willebrand Factor, vascular endothelial-cadherin and Flk-1[110-112]. These markers, in addition to CD133, and CD34 [113], allow HSCs to be distinguished from MSCs and other primitive cells[114]. Placement of CD34+ HSCs onto compatible POCfs improved neovascularization and reduced fibrosis when injected into the site of injury[115].

Angiogenesis in the diseased urethral sphincter is beneficial for two reasons. First, it will nourish the proliferation and regeneration of MSCs into muscular components. Second, the blood supply will contribute to the vascular plexus that surrounds the urethral smooth muscle lumen. This plexus, when perfused, helps forms a tight seal of the mucosal surfaces, just as muscle contraction would.

Addressing the need for neural components in tissue engineering has been challenging. One study from our own group demonstrated the ability of MSCs combined with CD34+ cells to form muscular, vascular and even neural tissue in a rat bladder augmentation model[115]. Stem/progenitor cells were seeded onto POC scaffolds prior to implantation, which yielded well-organized fascicles of smooth muscle supported by collagen. CD34+ cells contributed greatly to the levels and distribution of blood vessels in MSCs/CD34+/POC constructs. Novel to this study was the detection of peripheral nerve regeneration from the surrounding healthy tissue. Stained with neuronal specific antibodies βIII tubulin and synaptophysin, rat nerve bundles innervated the regenerated tissue significantly more in MSC/CD34+/POC grafts than in controls. The authors suggest that renewal of a blood supply to the area improves delivery of growth factors and cytokines promoting neuronal growth.

**CONCLUSION**

In the evolving field of tissue engineering, there has been an overwhelming trend towards therapy against the exact mechanism of disease causing SUI. Individual studies have lent credence to the importance of MSCs, CD34+ HSCs, scaffolds and growth factors in efforts to regenerate the urethral sphincter. A combination of these four components would create a plausible scenario in which to restore function in a structure as complex as the sphincter. Even with the advances in surgical slings, there still remains an inherent need to establish normal physiological function. Paired with POC scaffolds, we exploit the vast potential MSCs to differentiate into muscle, and hematopoietic precursors to proliferate into blood vessels in the presence of cytokines and growth factors. The indices of LPP readings from pre-operative urodynamic studies can be correlated to different levels of POCf elasticities, suited for a specific patient. Immunohistochemical and calcium release assays would support the MSC contractile properties as muscle regenerates, and nicotinic receptors targeted by α-bungarotoxin would illustrate the presence of neuronal fibers[116].

At least one study has observed the restoration of skeletal muscle and ganglionic elements from MSC injection into the rat urethral sphincter. Conducted by Kinebuchi *et al*[69], this study is a step in the right direction. However, follow up results did not confirm any improvement to LPP when compared to a control of cell free medium injection. The authors attribute the finding to inflammatory changes and to an insufficient bone marrow stem cells volume. In spite of this, the fallbacks can perhaps be accounted for by the absence of scaffolds and growth factors. Applications of this system expand beyond the treatment of SUI in adult women. Foremost, children born with neurogenic bladders secondary to myelomeningocele often have coexistent sphincter dysfunction. Likewise, post-prostatectomy men occasionally complain of incontinence as well. Patients with multiple sclerosis may have S2-S4 damage, leading to neuromuscular degeneration from the loss of incoming sensory nerve impulses and outgoing motor signals. The concept of urinary incontinence is similar to that of vesicoureteral reflux, so tissue engineering strategies provide an additional avenue to explore alongside ureteral reimplantation. To improve the symptoms of lower urinary tract symptoms in these patients, MSCs, HSCs, POC, and growth factors may one day supplement current surgical tactics.

**REFERENCES**

1 **Kapoor DS**, Meher S, Watkins L, Das M. Referral patterns for pelvic floor disorders. *Int Urogynecol J Pelvic Floor Dysfunct* 2009; **20**: 1469-1472 [PMID: 19657574 DOI: 10.1007/s00192-009-0972-0]

2 **Stothers L**, Friedman B. Risk factors for the development of stress urinary incontinence in women. *Curr Urol Rep* 2011; **12**: 363-369 [PMID: 21938471 DOI: 10.1007/s11934-011-0215-z]

3 **Milsom I**. Lower urinary tract symptoms in women. *Curr Opin Urol* 2009; **19**: 337-341 [PMID: 19444118 DOI: 10.1097/MOU.0b013e32832b659d]

4 **Strasser H**, Tiefenthaler M, Steinlechner M, Eder I, Bartsch G, Konwalinka G. Age dependent apoptosis and loss of rhabdosphincter cells. *J Urol* 2000; **164**: 1781-1785 [PMID: 11025769]

5 **Brown SJ**, Gartland D, Donath S, MacArthur C. Effects of prolonged second stage, method of birth, timing of caesarean section and other obstetric risk factors on postnatal urinary incontinence: an Australian nulliparous cohort study. *BJOG* 2011; **118**: 991-1000 [PMID: 21489125 DOI: 10.1111/j.1471-0528.2011.02928.x]

6 **Sajadi KP**, Gill BC, Damaser MS. Neurogenic aspects of stress urinary incontinence. *Curr Opin Obstet Gynecol* 2010; **22**: 425-429 [PMID: 20706117 DOI: 10.1097/GCO.0b013e32833e499d]

7 **Sangsawang B**, Sangsawang N. Stress urinary incontinence in pregnant women: a review of prevalence, pathophysiology, and treatment. *Int Urogynecol J* 2013; **24**: 901-912 [PMID: 23436035 DOI: 10.1007/s00192-013-2061-7]

8 **Aboushwareb T**, McKenzie P, Wezel F, Southgate J, Badlani G. Is tissue engineering and biomaterials the future for lower urinary tract dysfunction (LUTD)/pelvic organ prolapse (POP)? *Neurourol Urodyn* 2011; **30**: 775-782 [PMID: 21661029 DOI: 10.1002/nau.21101]

9 **Kim JC**, Cho KJ. Current trends in the management of post-prostatectomy incontinence. *Korean J Urol* 2012; **53**: 511-518 [PMID: 22949993 DOI: 10.4111/kju.2012.53.8.511]

10 **Visser E**, de Bock GH, Kollen BJ, Meijerink M, Berger MY, Dekker JH. Systematic screening for urinary incontinence in older women: who could benefit from it? *Scand J Prim Health Care* 2012; **30**: 21-28 [PMID: 22324458 DOI: 10.3109/02813432.2011.628244]

11 **Harris SS**, Link CL, Tennstedt SL, Kusek JW, McKinlay JB. Care seeking and treatment for urinary incontinence in a diverse population. *J Urol* 2007; **177**: 680-684 [PMID: 17222656 DOI: 10.1016/j.juro.2006.09.045]

12 **Papanicolaou S**, Hunskaar S, Lose G, Sykes D. Assessment of bothersomeness and impact on quality of life of urinary incontinence in women in France, Germany, Spain and the UK. *BJU Int* 2005; **96**: 831-838 [PMID: 16153212 DOI: 10.1111/j.1464-410X.2005.05722.x]

13 **Irwin DE**, Milsom I, Kopp Z, Abrams P, Cardozo L. Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. *BJU Int* 2006; **97**: 96-100 [PMID: 16336336 DOI: 10.1111/j.1464-410X.2005.05889.x]

14 **Brown WJ**, Miller YD. Too wet to exercise? Leaking urine as a barrier to physical activity in women. *J Sci Med Sport* 2001; **4**: 373-378 [PMID: 11905931]

15 **Coyne KS**, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. *Eur Urol* 2012; **61**: 88-95 [PMID: 21831517 DOI: S0302-2838(11)00787-1]

16 **Ko Y**, Lin SJ, Salmon JW, Bron MS. The impact of urinary incontinence on quality of life of the elderly. *Am J Manag Care* 2005; **11**: S103-S111 [PMID: 16161383]

17 **Beeckman D**, Verhaeghe S, Defloor T, Schoonhoven L, Vanderwee K. A 3-in-1 perineal care washcloth impregnated with dimethicone 3% versus water and pH neutral soap to prevent and treat incontinence-associated dermatitis: a randomized, controlled clinical trial. *J Wound Ostomy Continence Nurs* 2011; **38**: 627-634 [PMID: 21952346 DOI: 10.1097/WON.0b013e31822efe52]

18 **Tapia CI**, Khalaf K, Berenson K, Globe D, Chancellor M, Carr LK. Health-related quality of life and economic impact of urinary incontinence due to detrusor overactivity associated with a neurologic condition: a systematic review. *Health Qual Life Outcomes* 2013; **11**: 13 [PMID: 23369111 DOI: 10.1186/1477-7525-11-13]

19 **Tubaro A**, Puccini F, De Nunzio C, Digesu GA, Elneil S, Gobbi C, Khullar V. The treatment of lower urinary tract symptoms in patients with multiple sclerosis: a systematic review. *Curr Urol Rep* 2012; **13**: 335-342 [PMID: 22886612 DOI: 10.1007/s11934-012-0266-9]

20 **Murphy AM**, Bethoux F, Stough D, Goldman HB. Prevalence of stress urinary incontinence in women with multiple sclerosis. *Int Neurourol J* 2012; **16**: 86-90 [PMID: 22816049 DOI: 10.5213/inj.2012.16.2.86]

21 **Petros PE**, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. *Acta Obstet Gynecol Scand Suppl* 1990; **153**: 7-31 [PMID: 2093278]

22 **Ashton-Miller JA**, DeLancey JO. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci* 2007; **1101**: 266-296 [PMID: 17416924 DOI: annals.1389.034]

23 **DeLancey JO**. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol* 1994; **170**: 1713-120; discussion 1713-120; [PMID: 8203431]

24 **Wing RR**, West DS, Grady D, Creasman JM, Richter HE, Myers D, Burgio KL, Franklin F, Gorin AA, Vittinghoff E, Macer J, Kusek JW, Subak LL. Effect of weight loss on urinary incontinence in overweight and obese women: results at 12 and 18 months. *J Urol* 2010; **184**: 1005-1010 [PMID: 20643425 DOI: 10.1016/j.juro.2010.05.031]

25 **Wallace SA**, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. *Cochrane Database Syst Rev* 2004; : CD001308 [PMID: 14973967 DOI: 10.1002/14651858.CD001308.pub2]

26 **Shamliyan TA**, Kane RL, Wyman J, Wilt TJ. Systematic review: randomized, controlled trials of nonsurgical treatments for urinary incontinence in women. *Ann Intern Med* 2008; **148**: 459-473 [PMID: 18268288]

27 **Saks EK**, Arya LA. Pharmacologic management of urinary incontinence, voiding dysfunction, and overactive bladder. *Obstet Gynecol Clin North Am* 2009; **36**: 493-507 [PMID: 19932412 DOI: 10.1016/j.ogc.2009.08.001]

28 **Dumoulin C**, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev* 2010; : CD005654 [PMID: 20091581 DOI: 10.1002/14651858.CD005654.pub2]

29 **Smith AL**, Wein AJ. Urinary incontinence: pharmacotherapy options. *Ann Med* 2011; **43**: 461-476 [PMID: 21639723 DOI: 10.3109/07853890.2011.564203]

30 **Mariappan P**, Ballantyne Z, N'Dow JM, Alhasso AA. Serotonin and noradrenaline reuptake inhibitors (SNRI) for stress urinary incontinence in adults. *Cochrane Database Syst Rev* 2005; : CD004742 [PMID: 16034945 DOI: 10.1002/14651858.CD004742.pub2]

31 **Li J**, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. *Int Urol Nephrol* 2013; **45**: 679-686 [PMID: 23504618 DOI: 10.1007/s11255-013-0410-6]

32 **Deepak P**, Kumar TN, Sen TK. Evaluation of efficacy of duloxetine in stress urinary incontinence in women. *Indian J Pharmacol* 2011; **43**: 176-179 [PMID: 21572653 DOI: 10.4103/0253-7613.77357]

33 **Herbison P**, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *BMJ* 2003; **326**: 841-844 [PMID: 12702614 DOI: 10.1136/bmj.326.7394.841]

34 **Weber AM**, Walters MD. Cost-effectiveness of urodynamic testing before surgery for women with pelvic organ prolapse and stress urinary incontinence. *Am J Obstet Gynecol* 2000; **183**: 1338-146; discussion 1338-146; [PMID: 11120494 DOI: 10.1067/mob.2000.111251]

35 **Weber AM**, Taylor RJ, Wei JT, Lemack G, Piedmonte MR, Walters MD. The cost-effectiveness of preoperative testing (basic office assessment vs. urodynamics) for stress urinary incontinence in women. *BJU Int* 2002; **89**: 356-363 [PMID: 11872024]

36 **Koonings PP**, Bergman A, Ballard CA. Low urethral pressure and stress urinary incontinence in women: risk factor for failed retropubic surgical procedure. *Urology* 1990; **36**: 245-248 [PMID: 2392816]

37 **Jonsson Funk M**, Levin PJ, Wu JM. Trends in the surgical management of stress urinary incontinence. *Obstet Gynecol* 2012; **119**: 845-851 [PMID: 22433349 DOI: 10.1097/AOG.0b013e31824b2e3e]

38 **Ogah J**, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev* 2009; : CD006375 [PMID: 19821363 DOI: 10.1002/14651858.CD006375.pub2]

39 **Sarlos D**, Kuronen M, Schaer GN. How does tension-free vaginal tape correct stress incontinence? investigation by perineal ultrasound. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14**: 395-398 [PMID: 14677000 DOI: 10.1007/s00192-003-1103-y]

40 **Richter HE**, Albo ME, Zyczynski HM, Kenton K, Norton PA, Sirls LT, Kraus SR, Chai TC, Lemack GE, Dandreo KJ, Varner RE, Menefee S, Ghetti C, Brubaker L, Nygaard I, Khandwala S, Rozanski TA, Johnson H, Schaffer J, Stoddard AM, Holley RL, Nager CW, Moalli P, Mueller E, Arisco AM, Corton M, Tennstedt S, Chang TD, Gormley EA, Litman HJ. Retropubic versus transobturator midurethral slings for stress incontinence. *N Engl J Med* 2010; **362**: 2066-2076 [PMID: 20479459 DOI: NEJMoa0912658]

41 **Schierlitz L**, Dwyer PL, Rosamilia A, Murray C, Thomas E, De Souza A, Hiscock R. Three-year follow-up of tension-free vaginal tape compared with transobturator tape in women with stress urinary incontinence and intrinsic sphincter deficiency. *Obstet Gynecol* 2012; **119**: 321-327 [PMID: 22270284 DOI: 00006250-201202000-00018]

42 **Araco F**, Gravante G, Dati S, Bulzomi' V, Sesti F, Piccione E. Results 1 year after the Reemex system was applied for the treatment of stress urinary incontinence caused by intrinsic sphincter deficiency. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; **19**: 783-786 [PMID: 18071617 DOI: 10.1007/s00192-007-0523-5]

43 **Feki A**, Faltin DL, Lei T, Dubuisson JB, Jacob S, Irion O. Sphincter incontinence: is regenerative medicine the best alternative to restore urinary or anal sphincter function? *Int J Biochem Cell Biol* 2007; **39**: 678-684 [PMID: 17208507 DOI: S1357-2725(06)00317-7]

44 **Lapitan MC**, Cody DJ, Grant AM. Open retropubic colposuspension for urinary incontinence in women. *Cochrane Database Syst Rev* 2005; : CD002912 [PMID: 16034879 DOI: 10.1002/14651858.CD002912.pub2]

45 **Kammerer-Doak DN**, Cornella JL, Magrina JF, Stanhope CR, Smilack J. Osteitis pubis after Marshall-Marchetti-Krantz urethropexy: a pubic osteomyelitis. *Am J Obstet Gynecol* 1998; **179**: 586-590 [PMID: 9757956]

46 **Jankowski R**, Pruchnic R, Hiles M, Chancellor MB. Advances toward tissue engineering for the treatment of stress urinary incontinence. *Rev Urol* 2004; **6**: 51-57 [PMID: 16985578]

47 **VandeVord PJ**, Broadrick KM, Krishnamurthy B, Singla AK. A comparative study evaluating the in vivo incorporation of biological sling materials. *Urology* 2010; **75**: 1228-1233 [PMID: 19773037 DOI: 10.1016/j.urology.2009.06.046]

48 **Zoorob D**, Karram M. Role of autologous bladder-neck slings: a urogynecology perspective. *Urol Clin North Am* 2012; **39**: 311-316 [PMID: 22877713 DOI: 10.1016/j.ucl.2012.06.009]

49 **Carbone JM**, Kavaler E, Hu JC, Raz S. Pubovaginal sling using cadaveric fascia and bone anchors: disappointing early results. *J Urol* 2001; **165**: 1605-1611 [PMID: 11342927]

50 **Subak LL**, Brubaker L, Chai TC, Creasman JM, Diokno AC, Goode PS, Kraus SR, Kusek JW, Leng WW, Lukacz ES, Norton P, Tennstedt S. High costs of urinary incontinence among women electing surgery to treat stress incontinence. *Obstet Gynecol* 2008; **111**: 899-907 [PMID: 18378749 DOI: 10.1097/AOG.0b013e31816a1e12]

51 **Ugurlucan FG**, Erkan HA, Onal M, Yalcin O. Randomized trial of graft materials in transobturator tape operation: biological versus synthetic. *Int Urogynecol J* 2013; **24**: 1315-1323 [PMID: 23184140 DOI: 10.1007/s00192-012-2008-4]

52 **Brubaker L**, Norton PA, Albo ME, Chai TC, Dandreo KJ, Lloyd KL, Lowder JL, Sirls LT, Lemack GE, Arisco AM, Xu Y, Kusek JW. Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study. *Am J Obstet Gynecol* 2011; **205**: 498.e1-498.e6 [PMID: 21925636 DOI: 10.1016/j.ajog.2011.07.011]

53 **Filocamo MT**, Serati M, Frumenzio E, Li arzi V, Cattoni E, Champagne A, Salvatore S, Nicita G, Costantini E. The impact of mid-urethral slings for the treatment of urodynamic stress incontinence on female sexual function: a multicenter prospective study. *J Sex Med* 2011; **8**: 2002-2008 [PMID: 21762389 DOI: 10.1111/j.1743-6109.2011.02278.x]

54 **De Souza A**, Dwyer PL, Rosamilia A, Hiscock R, Lim YN, Murray C, Thomas E, Conway C, Schierlitz L. Sexual function following retropubic TVT and transobturator Monarc sling in women with intrinsic sphincter deficiency: a multicentre prospective study. *Int Urogynecol J* 2012; **23**: 153-158 [PMID: 21811769 DOI: 10.1007/s00192-011-1461-9]

55 **Jha S**, Ammenbal M, Metwally M. Impact of incontinence surgery on sexual function: a systematic review and meta-analysis. *J Sex Med* 2012; **9**: 34-43 [PMID: 21699671 DOI: 10.1111/j.1743-6109.2011.02366.x]

56 **Schulz JA**, Nager CW, Stanton SL, Baessler K. Bulking agents for stress urinary incontinence: short-term results and complications in a randomized comparison of periurethral and transurethral injections. *Int Urogynecol J Pelvic Floor Dysfunct* 2004; **15**: 261-265 [PMID: 15517671]

57 **Kuhn A**, Stadlmayr W, Lengsfeld D, Mueller MD. Where should bulking agents for female urodynamic stress incontinence be injected? *Int Urogynecol J Pelvic Floor Dysfunct* 2008; **19**: 817-821 [PMID: 18157642 DOI: 10.1007/s00192-007-0535-1]

58 **Zou XH**, Zhi YL, Chen X, Jin HM, Wang LL, Jiang YZ, Yin Z, Ouyang HW. Mesenchymal stem cell seeded knitted silk sling for the treatment of stress urinary incontinence. *Biomaterials* 2010; **31**: 4872-4879 [PMID: 20303586 DOI: S0142-9612(10)00302-9]

59 **Hong SH**, Piao S, Kim IG, Lee JY, Cho HJ, Kim SW, Hwang TK, Lee JY. Comparison of three types of stress urinary incontinence rat models: electrocauterization, pudendal denervation, and vaginal distension. *Urology* 2013; **81**: 465.e1-465.e6 [PMID: 23374842 DOI: 10.1016/j.urology.2012.10.029]

60 **Hussain M**, Greenwell TJ, Venn SN, Mundy AR. The current role of the artificial urinary sphincter for the treatment of urinary incontinence. *J Urol* 2005; **174**: 418-424 [PMID: 16006857 DOI: 10.1097/01.ju.0000165345.11199.98]

61 **Lipp A**, Shaw C, Glavind K. Mechanical devices for urinary incontinence in women. *Cochrane Database Syst Rev* 2011; : CD001756 [PMID: 21735385 DOI: 10.1002/14651858.CD001756.pub5]

62 **Sèbe P**, Doucet C, Cornu JN, Ciofu C, Costa P, de Medina SG, Pinset C, Haab F. Intrasphincteric injections of autologous muscular cells in women with refractory stress urinary incontinence: a prospective study. *Int Urogynecol J* 2011; **22**: 183-189 [PMID: 20821309 DOI: 10.1007/s00192-010-1255-5]

63 **Lin G**, Wang G, Banie L, Ning H, Shindel AW, Fandel TM, Lue TF, Lin CS. Treatment of stress urinary incontinence with adipose tissue-derived stem cells. *Cytotherapy* 2010; **12**: 88-95 [PMID: 19878076 DOI: 10.3109/14653240903350265]

64 **Jack GS**, Almeida FG, Zhang R, Alfonso ZC, Zuk PA, Rodríguez LV. Processed lipoaspirate cells for tissue engineering of the lower urinary tract: implications for the treatment of stress urinary incontinence and bladder reconstruction. *J Urol* 2005; **174**: 2041-2045 [PMID: 16217390 DOI: S0022-5347(01)68884-0]

65 **Obinata D**, Matsumoto T, Ikado Y, Sakuma T, Kano K, Fukuda N, Yamaguchi K, Mugishima H, Takahashi S. Transplantation of mature adipocyte-derived dedifferentiated fat (DFAT) cells improves urethral sphincter contractility in a rat model. *Int J Urol* 2011; **18**: 827-834 [PMID: 21991997 DOI: 10.1111/j.1442-2042.2011.02865.x]

66 **Chun SY**, Cho DH, Chae SY, Choi KH, Lim HJ, Yoon GS, Kim BS, Kim BW, Yoo JJ, Kwon TG. Human amniotic fluid stem cell-derived muscle progenitor cell therapy for stress urinary incontinence. *J Korean Med Sci* 2012; **27**: 1300-1307 [PMID: 23166409 DOI: 10.3346/jkms.2012.27.11.1300]

67 **Kwon D**, Kim Y, Pruchnic R, Jankowski R, Usiene I, de Miguel F, Huard J, Chancellor MB. Periurethral cellular injection: comparison of muscle-derived progenitor cells and fibroblasts with regard to efficacy and tissue contractility in an animal model of stress urinary incontinence. *Urology* 2006; **68**: 449-454 [PMID: 16904482 DOI: S0090-4295(06)00386-4]

68 **Imamura T**, Ishizuka O, Kinebuchi Y, Kurizaki Y, Nakayama T, Ishikawa M, Nishizawa O. Implantation of autologous bone-marrow-derived cells reconstructs functional urethral sphincters in rabbits. *Tissue Eng Part A* 2011; **17**: 1069-1081 [PMID: 21091339 DOI: 10.1089/ten.TEA.2010.0478]

69 **Kinebuchi Y**, Aizawa N, Imamura T, Ishizuka O, Igawa Y, Nishizawa O. Autologous bone-marrow-derived mesenchymal stem cell transplantation into injured rat urethral sphincter. *Int J Urol* 2010; **17**: 359-368 [PMID: 20202003 DOI: IJU2471]

70 **Mitterberger M**, Marksteiner R, Margreiter E, Pinggera GM, Frauscher F, Ulmer H, Fussenegger M, Bartsch G, Strasser H. Myoblast and fibroblast therapy for post-prostatectomy urinary incontinence: 1-year followup of 63 patients. *J Urol* 2008; **179**: 226-231 [PMID: 18001790 DOI: 10.1016/j.juro.2007.08.154]

71 **Gerullis H**, Eimer C, Georgas E, Homburger M, El-Baz AG, Wishahi M, Borós M, Ecke TH, Otto T. Muscle-derived cells for treatment of iatrogenic sphincter damage and urinary incontinence in men. *ScientificWorldJournal* 2012; **2012**: 898535 [PMID: 22919359 DOI: 10.1100/2012/898535]

72 **Corcos J**, Loutochin O, Campeau L, Eliopoulos N, Bouchentouf M, Blok B, 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 [PMID: 21412824 DOI: 10.1002/nau.20998]

73 **Kassem M**, Kristiansen M, Abdallah BM. Mesenchymal stem cells: cell biology and potential use in therapy. *Basic Clin Pharmacol Toxicol* 2004; **95**: 209-214 [PMID: 15546474 DOI: PTOpto950502]

74 **Drewa T**, Adamowicz J, Sharma A. Tissue engineering for the oncologic urinary bladder. *Nat Rev Urol* 2012; **9**: 561-572 [PMID: 22907387 DOI: 10.1038/nrurol.2012.158]

75 **Dayanc M**, Kibar Y, Ural AU, Onguru O, Yildiz O, Irkilata HC, Avcu F, Soner BC, Ulku C, Seyrek M. The histopathologic, pharmacologic and urodynamic results of mesenchymal stem cell's injection into the decompensated rabbit's bladder. *Stem Cell Rev* 2012; **8**: 1245-1253 [PMID: 22736388 DOI: 10.1007/s12015-012-9393-4]

76 **Sharma AK**, Bury MI, Marks AJ, Fuller NJ, Meisner JW, Tapaskar N, Halliday LC, Matoka DJ, Cheng EY. A nonhuman primate model for urinary bladder regeneration using autologous sources of bone marrow-derived mesenchymal stem cells. *Stem Cells* 2011; **29**: 241-250 [PMID: 21732482 DOI: 10.1002/stem.568]

77 **Woo LL**, Tanaka ST, Anumanthan G, Pope JC, Thomas JC, Adams MC, Brock JW, Bhowmick NA. Mesenchymal stem cell recruitment and improved bladder function after bladder outlet obstruction: preliminary data. *J Urol* 2011; **185**: 1132-1138 [PMID: 21255803 DOI: 10.1016/j.juro.2010.10.033]

78 **Drzewiecki BA**, Thomas JC, Tanaka ST. Bone marrow-derived mesenchymal stem cells: current and future applications in the urinary bladder. *Stem Cells Int* 2011; **2010**: 765167 [PMID: 21253479 DOI: 10.4061/2010/765167]

79 **Lane FL**, Jacobs S. Stem cells in gynecology. *Am J Obstet Gynecol* 2012; **207**: 149-156 [PMID: 22464292 DOI: 10.1016/j.ajog.2012.01.045]

80 **Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

81 **Ryan JM**, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. *J Inflamm (Lond)* 2005; **2**: 8 [PMID: 16045800 DOI: 1476-9255-2-8]

82 **Tse WT**, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation* 2003; **75**: 389-397 [PMID: 12589164 DOI: 10.1097/01.TP.0000045055.63901.A9]

83 **Sekiya I**, Larson BL, Smith JR, Pochampally R, Cui JG, Prockop DJ. Expansion of human adult stem cells from bone marrow stroma: conditions that maximize the yields of early progenitors and evaluate their quality. *Stem Cells* 2002; **20**: 530-541 [PMID: 12456961 DOI: 10.1634/stemcells.20-6-530]

84 **Pittenger MF**, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999; **284**: 143-147 [PMID: 10102814]

85 **Aggarwal S**, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005; **105**: 1815-1822 [PMID: 15494428 DOI: 2004-04-1559]

86 **Ishikane S**, Ohnishi S, Yamahara K, Sada M, Harada K, Mishima K, Iwasaki K, Fujiwara M, Kitamura S, Nagaya N, Ikeda T. Allogeneic injection of fetal membrane-derived mesenchymal stem cells induces therapeutic angiogenesis in a rat model of hind limb ischemia. *Stem Cells* 2008; **26**: 2625-2633 [PMID: 18669910 DOI: 10.1634/stemcells.2008-0236]

87 **Anumanthan G**, Makari JH, Honea L, Thomas JC, Wills ML, Bhowmick NA, Adams MC, Hayward SW, Matusik RJ, Brock JW, Pope JC. Directed differentiation of bone marrow derived mesenchymal stem cells into bladder urothelium. *J Urol* 2008; **180**: 1778-1783 [PMID: 18721942 DOI: S0022-5347(08)01140-3]

88 **Tian H**, Bharadwaj S, Liu Y, Ma PX, Atala A, Zhang Y. Differentiation of human bone marrow mesenchymal stem cells into bladder cells: potential for urological tissue engineering. *Tissue Eng Part A* 2010; **16**: 1769-1779 [PMID: 20020816 DOI: 10.1089/ten.TEA.2009.0625]

89 **Surcel C**, Savu C, Chibelean C, Iordache A, Mirvald C, Sinescu I. Comparative analysis of different surgical procedures for female stress urinary incontinence. Is stem cell implantation the future? *Rom J Morphol Embryol* 2012; **53**: 151-154 [PMID: 22395514]

90 **Carr LK**, Steele D, Steele S, Wagner D, Pruchnic R, Jankowski R, Erickson J, Huard J, Chancellor MB. 1-year follow-up of autologous muscle-derived stem cell injection pilot study to treat stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; **19**: 881-883 [PMID: 18204978 DOI: 10.1007/s00192-007-0553-z]

91 Peters K, Kaufman M, Dmochowski R, Carr L, Herschorn S, Fischer M, Sirls L, Nagaraju P, Biller D, Ward R, Chancellor M. 1340 AUTOLOGOUS MUSCLE DERIVED CELL THERAPY FOR THE TREATMENT OF FEMALE STRESS URINARY INCONTINENCE: A MULTI-CENTER EXPERIENCE. The Journal of Urology, 2011: 535-536

92 **Beauchamp JR**, Morgan JE, Pagel CN, Partridge TA. Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source. *J Cell Biol* 1999; **144**: 1113-1122 [PMID: 10087257]

93 **Zhao W**, Zhang C, Jin C, Zhang Z, Kong D, Xu W, Xiu Y. Periurethral injection of autologous adipose-derived stem cells with controlled-release nerve growth factor for the treatment of stress urinary incontinence in a rat model. *Eur Urol* 2011; **59**: 155-163 [PMID: 21050657 DOI: S0302-2838(10)01003-1]

94 **Cho ER**, Kang SW, Park HJ, Cho YS, Lee YS, Kim JC, Kim BS. Submucosal injection of poly(lactic-co-glycolic acid) microspheres in rabbit bladder as a potential treatment for urinary incontinence and vesicoureteral reflux: preliminary results. *J Biomater Sci Polym Ed* 2005; **16**: 1109-1120 [PMID: 16231602]

95 **Oh SH**, Lee JY, Ghil SH, Lee SS, Yuk SH, Lee JH. PCL microparticle-dispersed PLGA solution as a potential injectable urethral bulking agent. *Biomaterials* 2006; **27**: 1936-1944 [PMID: 16221494 DOI: S0142-9612(05)00870-7]

96 **Selim M**, Bullock AJ, Blackwood KA, Chapple CR, MacNeil S. Developing biodegradable scaffolds for tissue engineering of the urethra. *BJU Int* 2011; **107**: 296-302 [PMID: 20477828 DOI: 10.1111/j.1464-410X.2010.09310.x]

97 Webb A, Kumar, VA, Ameer GA. Biodegradable poly(diol citrate) nanocomposite elastomers for soft tissue engineering. J. Mater. Chem, 2007: 900-906

98 **Sharma AK**, Hota PV, Matoka DJ, Fuller NJ, Jandali D, Thaker H, Ameer GA, Cheng EY. Urinary bladder smooth muscle regeneration utilizing bone marrow derived mesenchymal stem cell seeded elastomeric poly(1,8-octanediol-co-citrate) based thin films. *Biomaterials* 2010; **31**: 6207-6217 [PMID: 20488535 DOI: S0142-9612(10)00570-3]

99 **Sharma AK**, Bury MI, Fuller NJ, Rozkiewicz DI, Hota PV, Kollhoff DM, Webber MJ, Tapaskar N, Meisner JW, Lariviere PJ, Destefano S, Wang D, Ameer GA, Cheng EY. Growth factor release from a chemically modified elastomeric poly(1,8-octanediol-co-citrate) thin film promotes angiogenesis in vivo. *J Biomed Mater Res A* 2012; **100**: 561-570 [PMID: 22162300 DOI: 10.1002/jbm.a.33306]

100 **Lenis AT**, Kuang M, Woo LL, Hijaz A, Penn MS, Butler RS, Rackley R, Damaser MS, Wood HM. Impact of parturition on chemokine homing factor expression in the vaginal distention model of stress urinary incontinence. *J Urol* 2013; **189**: 1588-1594 [PMID: 23022009 DOI: 10.1016/j.juro.2012.09.096]

101 **Cruz M**, Dissaranan C, Cotleur A, Kiedrowski M, Penn M, Damaser M. Pelvic organ distribution of mesenchymal stem cells injected intravenously after simulated childbirth injury in female rats. *Obstet Gynecol Int* 2012; **2012**: 612946 [PMID: 21941558 DOI: 10.1155/2012/612946]

102 **Papayannopoulou T**, Priestley GV, Bonig H, Nakamoto B. The role of G-protein signaling in hematopoietic stem/progenitor cell mobilization. *Blood* 2003; **101**: 4739-4747 [PMID: 12595315 DOI: 10.1182/blood-2002-09-2741]

103 Dissaranan C, Cruz M, Gill B, Salcedo L, Cotleur A, Mendieta R, Balog B, Kiedrowski M, Penn M, Goldman H, Damaser M. 176 intravenous mesenchymal stem cells home to the urethra and facilitate recovery from stress urinary incontinence after childbirth injury via local secretion of paracrine factors. *J Urol* 2011: 73

104 **Yiou R**, Lefaucheur JP, Atala A. The regeneration process of the striated urethral sphincter involves activation of intrinsic satellite cells. *Anat Embryol (Berl)* 2003; **206**: 429-435 [PMID: 12728313 DOI: 10.1007/s00429-003-0313-x]

105 **Delo DM**, Eberli D, Williams JK, Andersson KE, Atala A, Soker S. Angiogenic gene modification of skeletal muscle cells to compensate for ageing-induced decline in bioengineered functional muscle tissue. *BJU Int* 2008; **102**: 878-884 [PMID: 18489526 DOI: 10.1111/j.1464-410X.2008.07750.x]

106 **Takahashi S**, Chen Q, Ogushi T, Fujimura T, Kumagai J, Matsumoto S, Hijikata S, Tabata Y, Kitamura T. Periurethral injection of sustained release basic fibroblast growth factor improves sphincteric contractility of the rat urethra denervated by botulinum-a toxin. *J Urol* 2006; **176**: 819-823 [PMID: 16813954 DOI: 10.1016/j.juro.2006.03.070]

107 **Meirelles Lda S**, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine Growth Factor Rev* 2009; **20**: 419-427 [PMID: 19926330 DOI: S1359-6101(09)00077-X]

108 **Hung SC**, Pochampally RR, Chen SC, Hsu SC, Prockop DJ. Angiogenic effects of human multipotent stromal cell conditioned medium activate the PI3K-Akt pathway in hypoxic endothelial cells to inhibit apoptosis, increase survival, and stimulate angiogenesis. *Stem Cells* 2007; **25**: 2363-2370 [PMID: 17540857 DOI: 10.1634/stemcells.2006-0686]

109 **Choi SJ**, Oh SH, Kim IG, Chun SY, Lee JY, Lee JH. Functional recovery of urethra by plasmid DNA-loaded injectable agent for the treatment of urinary incontinence. *Biomaterials* 2013; **34**: 4766-4776 [PMID: 23545290 DOI: 10.1016/j.biomaterials.2013.03.045]

110 **Baum CM**, Weissman IL, Tsukamoto AS, Buckle AM, Peault B. Isolation of a candidate human hematopoietic stem-cell population. *Proc Natl Acad Sci U S A* 1992; **89**: 2804-2808 [PMID: 1372992]

111 **Yang J**, Ii M, Kamei N, Alev C, Kwon SM, Kawamoto A, Akimaru H, Masuda H, Sawa Y, Asahara T. CD34+ cells represent highly functional endothelial progenitor cells in murine bone marrow. *PLoS One* 2011; **6**: e20219 [PMID: 21655289 DOI: PONE-D-10-06134]

112 **Asahara T**, Isner JM. Endothelial progenitor cells for vascular regeneration. *J Hematother Stem Cell Res* 2002; **11**: 171-178 [PMID: 11983091 DOI: 10.1089/152581602753658385]

113 **Yin AH**, Miraglia S, Zanjani ED, Almeida-Porada G, Ogawa M, Leary AG, Olweus J, Kearney J, Buck DW. AC133, a novel marker for human hematopoietic stem and progenitor cells. *Blood* 1997; **90**: 5002-5012 [PMID: 9389720]

114 **Ghajar CM**, Blevins KS, Hughes CC, George SC, Putnam AJ. Mesenchymal stem cells enhance angiogenesis in mechanically viable prevascularized tissues via early matrix metalloproteinase upregulation. *Tissue Eng* 2006; **12**: 2875-2888 [PMID: 17518656 DOI: 10.1089/ten.2006.12.2875]

115 **Sharma AK**, Bury MI, Fuller NJ, Marks AJ, Kollhoff DM, Rao MV, Hota PV, Matoka DJ, Edassery SL, Thaker H, Sarwark JF, Janicki JA, Ameer GA, Cheng EY. Cotransplantation with specific populations of spina bifida bone marrow stem/progenitor cells enhances urinary bladder regeneration. *Proc Natl Acad Sci U S A* 2013; **110**: 4003-4008 [PMID: 23431178 DOI: 10.1073/pnas.1220764110]

116 **Biérinx AS**, Sebille A. The urethral striated sphincter in adult male rat. *Anat Embryol (Berl)* 2006; **211**: 435-441 [PMID: 16633819 DOI: 10.1007/s00429-006-0093-1]

117 **Lee JY**, Cannon TW, Pruchnic R, Fraser MO, Huard J, Chancellor MB. The effects of periurethral muscle-derived stem cell injection on leak point pressure in a rat model of stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; **14**: 31-7; discussion 37 [PMID: 12601514 DOI: 10.1007/s00192-002-1004-5]

118 **Fu Q**, Song XF, Liao GL, Deng CL, Cui L. Myoblasts differentiated from adipose-derived stem cells to treat stress urinary incontinence. *Urology* 2010; **75**: 718-723 [PMID: 19969332 DOI: 10.1016/j.urology.2009.10.003]

119 **Lim JJ**, Jang JB, Kim JY, Moon SH, Lee CN, Lee KJ. Human umbilical cord blood mononuclear cell transplantation in rats with intrinsic sphincter deficiency. *J Korean Med Sci* 2010; **25**: 663-670 [PMID: 20436699 DOI: 10.3346/jkms.2010.25.5.663]

120 **Kim SO**, Na HS, Kwon D, Joo SY, Kim HS, Ahn Y. Bone-marrow-derived mesenchymal stem cell transplantation enhances closing pressure and leak point pressure in a female urinary incontinence rat model. *Urol Int* 2011; **86**: 110-116 [PMID: 20689260 DOI: 10.1159/000317322]

121 **Watanabe T**, Maruyama S, Yamamoto T, Kamo I, Yasuda K, Saka Y, Ozaki T, Yuzawa Y, Matsuo S, Gotoh M. Increased urethral resistance by periurethral injection of low serum cultured adipose-derived mesenchymal stromal cells in rats. *Int J Urol* 2011; **18**: 659-666 [PMID: 21707765 DOI: 10.1111/j.1442-2042.2011.02795.x]

122 **Kim BS**, Chun SY, Lee JK, Lim HJ, Bae JS, Chung HY, Atala A, Soker S, Yoo JJ, Kwon TG. Human amniotic fluid stem cell injection therapy for urethral sphincter regeneration in an animal model. *BMC Med* 2012; **10**: 94 [PMID: 22906045 DOI: 10.1186/1741-7015-10-94]

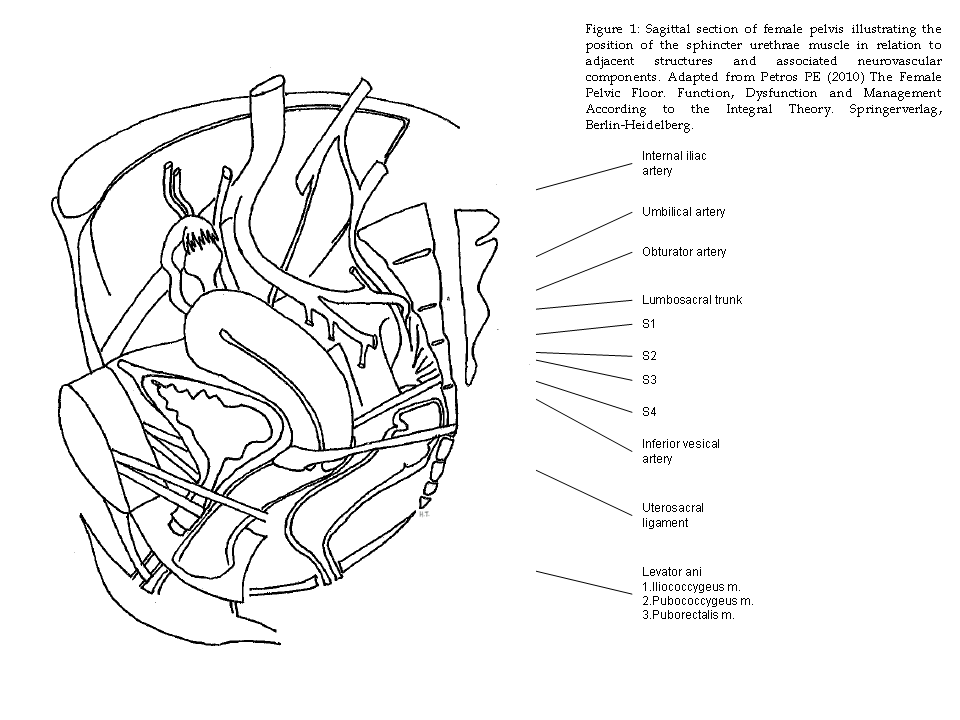
123 **Li GY**, Zhou F, Gong YQ, Cui WS, Yuan YM, Song WD, Xin H, Liu T, Li WR, Gao ZZ, Liu J, Guo YL, Xin ZC. Activation of VEGF and ERK1/2 and improvement of urethral function by adipose-derived stem cells in a rat stress urinary incontinence model. *Urology* 2012; **80**: 953.e1-953.e8 [PMID: 22950999 DOI: 10.1016/j.urology.2012.05.030]

124 **Lecoeur C**, Swieb S, Zini L, Rivière C, Combrisson H, Ghérardi R, Abbou C, Yiou R. Intraurethral transfer of satellite cells by myofiber implants results in the formation of innervated myotubes exerting tonic contractions. *J Urol* 2007; **178**: 332-337 [PMID: 17507041 DOI: 10.1016/j.juro.2007.02.044]

125 **Mitterberger M**, Marksteiner R, Margreiter E, Pinggera GM, Colleselli D, Frauscher F, Ulmer H, Fussenegger M, Bartsch G, Strasser H. Autologous myoblasts and fibroblasts for female stress incontinence: a 1-year follow-up in 123 patients. *BJU Int* 2007; **100**: 1081-1085 [PMID: 17760890 DOI: 10.1111/j.1464-410X.2007.07119.x]

126 **Mitterberger M**, Pinggera GM, Marksteiner R, Margreiter E, Fussenegger M, Frauscher F, Ulmer H, Hering S, Bartsch G, Strasser H. Adult stem cell therapy of female stress urinary incontinence. *Eur Urol* 2008; **53**: 169-175 [PMID: 17683852 DOI: 10.1016/j.eururo.2007.07.026]

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**Figure 1 Sagittal section of female pelvis illustrating the position of the sphincter urethrae muscle in relation to adjacent structures and associated neurovascular components.** Adapted from reference [21].

**Table 1 Periurethral stem/progenitor cell injections improving leak point and urethral closure pressures in various studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Stem/progenitor cell source** | | | **SUI model** | **LPP findings in cm H2O at 4 wk status post injection** | **Absolute difference in LPP in cm H2O and percent improvement** |
| Lee *et al*[117] | Allogenic gastrocnemius muscle derived stem cells (MDSC) | | | Rat, sciatic nerve transection | MDSC = 44.1 *±* 6.6  Saline = 18.6 *±* 5.2  Control (-) = 25.8 *±* 2.5 | MDSC = 18.3 ± 9.1, 70.93% |
| Kwon *et al*[67] | Muscle derived cells and fibroblasts | | | Rats, sciatic nerve transection | MDSC = 38.2 *±* 4.3  Fibroblast = 38.8 *±* 1.2  MDSC/fibroblast = 34.5 *±* 3.3  Control (-) = 25.8 *±* 1.4  Control (+) = 43.3 *±* 2.5 | MDSC = 12.4 ± 5.7, 48.06% Fibroblast = 13.0 ± 2.6, 50.38% MDSC/Fibroblast = 8.7 ± 4.7, 33.72% |
| Fu *et al*[118] | Adipose derived stem cells induced into myoblasts with 5-azacytidine | | | Rats, vaginal balloon dilation | Myoblast = 32.43 *±* 2.05  Adipose derived stem cells (ADSCs) = 30.75 *±* 3.17  Control (-) = 36.19 *±* 2.25  Control (+) = 45.42 *±* 1.71 | Myoblast = -3.76 ± 4.3, -10.38% ADSC = -5.44 ± 5.42, -15.03% |
| Kinebuchi *et al*[69] | Bone marrow derived mesenchymal stem cells | | | Rats, urethrolysis and cardiotoxic injection | Bone marrow stem cells (BMSC) = 25.66 *±* 4.38  Control (-) = 18.19 *±* 1.55  Control (+) = 35.98 *±* 5.14 | BMSC = 7.47 ± 5.93, 41.06% |
| Lim *et al*[119] | Human umbilical cord blood mononuclear cells | | | Rats, electrocauterization of periurethral soft tissue | Human umbilical cord serum (HUCS) = 91.75 *±* 18.99  Control (-) = 65.02 *±* 22.09 | HUCS = 26.76 ± 41.08, 41.16% |
| Kim *et al*[120] | Allogenic mesenchymal stem cells | | | Rats, pudendal nerve transection | MSC = 43.1 *±* 3.2  Control (-) = 22.0 *±* 2.2  Control (+) = 29.1 *±* 2.1 | MSC: 21.1 ± 5.4, 95.90% |
| Zhao *et al* [93] | Autologous adipose derived stem cells + nerve growth factor (NGF) | | | Rats, pudendal nerve transection | ADSC/poly(lactic-co-glycolic acid) (PLGA) = 17.8 *±* 3.1  ADSC/NGF = 18.3 *±* 2.4  ADSC/PLGA/NGF = 22.5 *±* 6.1  Control (-) = 11.6 *±* 2.7 | ADSC/PLGA = 6.2 ± 5.8, 53.44% ADSC/NGF = 6.7 ± 5.1, 57.75% ADSC/PLGA/NGF = 10.9 ± 8.8, 93.96% |
| Corcos *et al* [72] | Bone marrow derived mesenchymal stem cells | | | Rats, pudendal nerve transection | MSC = 24.28 *±* 1.47  Control (-) = 16.21 *±* 1.26 | MSC = 8.07 ± 2.73, 49.78% |
| Watanabe *et al*[121] | Adipose derived mesenchymal stem cells | | | Rats, pelvic nerve transection | Subtracted LPPs:  Collagen = 9.39 *±* 2.08  ASC = 8.86 *±* 3.13  Control (-) = 10.94 *±* 3.55 |  |
| Kim *et al*[122] | Human amniotic fluid stem cells | | | Rats, pudendal nerve transection | Human amniotic fluid cells (hAFCs) = 20.2 *±* 3.3  Control (-) = 15.2 *±* 3.1  Control (+) = 27.6 *±* 3.6 | hAFCs = 5.0 ± 6.4, 32.89% |
| Li *et al*[123] | Adipose derived stem cells | | | Rats, vaginal balloon dilation | ADSC = 46.34 *±* 2.63  Control (-) = 36.82 *±* 1.68  Control (+) = 48.92 *±* 2.71 | ADSC = 9.52 ± 4.31, 25.85% |
| Chun *et al*[66] | Human amniotic fluid stem cells | | | Rats, pudendal nerve transection | hAFCs = 23.9 *±* 1.85  Muscle progenitors = 38.43 *±* 0.51  Control (-) = 15.24 *±* 1.87  Control (+) = 36.54 *±* 1.67 | hAFCs = 8.66 ± 3.72, 56.82% Muscle progenitors = 23.19 ± 2.38, 152.16% |
| Lecoeur *et al*[124] | | Myofiber core of satellite cells | Pigs, endoscopic destruction of striated urethral sphincter | | Myofiber = 71.5 *±* 17.8  Curarization sphincter = 33.5 *±* 14.8 |  |
| Mitterberger *et al*[125] | | Autologous myoblasts and fibroblasts | Humans (*n* = 123) | | Pre-operative urine cystein protease (UCP) = 28.8 *±* 12.3  Post-operative UCP = 40.5 *±* 15.8  After 1 year | 11.7 ± 28.1, 40.62% |
| Mitterberger *et al*[126] | | Autologous myoblasts and fibroblasts | Humans (*n* = 20) | | Pre-operative UCP = 27.0 *±* 13.3  Post-operative UCP (1 yr) = 39.4 *±* 14.8  Post-operative UCP (2 yr) = 42.2 *±* 12.1 | 66.4 ± 28.1, 45.92% (1 yr) 15.2 ± 25.4, 56.29% |