

Cellular regenerative therapy in stress urinary incontinence: new frontiers? – a narrative review

Karl-Erik Andersson^{1,2^}, Kouidy Williams¹

¹Wake Forest Institute for Regenerative Medicine, Wake Forest Baptist Medical Center, Winston-Salem, NC, USA; ²Institute for Laboratory Medicine, Lund University, Lund, Sweden

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Correspondence to: Karl-Erik Andersson, MD, PhD, MA. Institute of Laboratory Medicine, Lund University, Sölvegatan 19, 221 00, Lund, Sweden; Wake Forest Institute for Regenerative Medicine, Wake Forest Baptist Medical Center, Winston-Salem, NC, USA. Email: karl-erik.andersson@med.lu.se.

Background and Objective: Even if treatment with stem cells has been shown to be safe and effective in many patients with stress urinary incontinence (SUI), there is still room for improvement using other regenerative medicine alternatives. Since the beneficial effects of stem cells are probably mediated by secretion of factors rather than by the cells themselves there is a good rationale for further exploring the therapeutic effects of the secretome and/or its components. However, homing factors such as stromal derived growth factor 1 (SDF-1; CXCL12), stimulation of stem cell growth and stem cell mobilization *in vivo* using low intensity shock wave therapy (Li-ESWT) or regenerative electrical stimulation (RES), are also promising approaches

Methods: A literature search was performed based on PubMed, Scopus and Google Scholar. The search criteria included original basic science articles, systematic reviews and randomized control trials. All studies were published between 2000 and 2023. Selected, peer-reviewed studies were further analyzed to identify those of relevance. Keywords searched included: “female stress incontinence”, “homing factors”, “CXCL12”, “secretome”, “low intensity shockwave therapy” and “regenerative electrical stimulation”. The peer-reviewed publications on the key word subjects that contained a novel addition to the existing body of literature were included.

Key Content and Findings: There is evidence from studies on non-human primates (NHPs) with experimental urinary sphincter injury that CXCL12 can restore sphincter structure and function. Studies with homing factors in human patients with SUI are still to be performed. A large number of clinical studies on the use of secretome or secretome products from mesenchymal stem cells (MSCs) on indications other than human SUI are already available. However, controlled clinical trials on patients with SUI, have to the best of our knowledge, not yet been performed. Also, RES has not been studied in patients with SUI. In contrast, there is clinical evidence that Li-ESWT may improve female SUI.

Conclusions: Treatment with homing factors, MSC secretome/secretome components, Li-ESWT and RES are promising frontiers in the treatment of human SUI caused by sphincter damage.

Keywords: Homing factors; CXCL12; secretome; conditioned medium (CM); low intensity shock wave therapy (Li-ESWT)

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[^] ORCID: 0000-0003-0665-3486.

Introduction

The pathophysiology of female stress urinary incontinence (SUI) is multifactorial. It may involve loss of urethral sphincter muscle function, but often decreased support of the pelvic floor and vaginal connective tissue around the bladder neck and urethra can be important contributors (1). Drug therapy (including duloxetine; not approved in the US) has limited efficacy and frequent adverse effects (2). Current surgical treatment is efficacious, but is also limited by adverse events such as complications with implanted permanent synthetic meshes and postoperative voiding dysfunction. This and the unfavorable long-term recurrence rates have led to a quest for the development of new non-surgical approaches. Stem cell therapy (SCT) seems a promising strategy for restoring urethral sphincter function in patients with SUI (3-6), and in a recent systematic review of the clinical trials available on SCT for SUI in woman, Klapper-Goldstein *et al.* (5) concluded that this therapy is safe and effective and gives promise for the future. Mariotti *et al.* (6) performed a systematic review and meta-analysis of 12 clinical trials and found a 41% mean rate of continence recovery with the use of autologous muscle derived (MDSC) or adipose derived stem cells (ADSCs). However, cell therapy still has some challenges (7), and there seems to be room for improvements.

The ability of mesenchymal stem cells (MSCs) to self-renew, to form clonal cell populations and to differentiate into multiple cell lineages is well established. The cells have anti-fibrotic, angiogenic, and anti-apoptotic properties and these properties are particularly attractive for restoring function in damaged tissues as in SUI. It was originally believed that e.g., autologous MSCs, engrafted or differentiated into injured host tissue. However, it is now well established that MSCs secrete soluble factors through a paracrine mechanism, which is believed to provide the therapeutic regenerative effect (8,9). Among the secreted factors are e.g., cytokines, such as stromal derived growth factor 1 (SDF-1; CXCL12), which are believed to act as homing factors, attracting cells from the circulation and/or the bone marrow to the site of damage where they repair tissues and restore function (10).

Stem cells may also exert a significant therapeutic effect by secreting packages of bioactive factors—the “secretome”—producing their anti-fibrotic, angiogenic, and anti-apoptotic properties (8-13). The effects of Li-ESWT on stem cells in culture suggest that it may be used as a non-invasive method to stimulate cell growth and mobilization

in vivo. Supporting this, recent clinical evidence (14) suggests that Li-ESWT could serve as a potentially novel treatment for SUI. Even if regenerative electrical stimulation (RES) has not been tested clinically for SUI treatment it may open new therapeutic opportunities.

Is the therapeutic use of cytokines, secretome/secretome components, Li-ESWT and RES new therapeutic frontiers for management of SUI? The aim of the present review is to give an update on recent information as an answer to this question. We present this article in accordance with the Narrative Review reporting checklist (<https://tau.amegroups.com/article/view/10.21037/tau-22-682/rc>).

Methods

Using PubMed, Google Scholar and Scopus, a comprehensive literature search was performed. In *Table 1*, the search strategy for articles included is given. Peer-reviewed original articles and reviews and randomized controlled clinical trials (when available), published between 2000 and 2023, were analyzed to identify articles of relevance. The keywords searched included: “female stress incontinence”, “homing factors”, “CXCL12”, “secretome”, “low energy shockwave therapy” and “regenerative electrical stimulation”. Publications that contained information that added to the existing body of literature within the field were included.

Discussion

Promise of “homing factors”

Karp and Leng Teo (15) defined MSC homing “as the arrest of MSCs within the vasculature of a tissue followed by transmigration across the endothelium”. A more recent definition was given by Liesveld *et al.* (16): “Stem cell homing refers to the ability of circulating stem cells or exogenously administered stem cells to locate and enter an environmental niche.” It has been shown that stem cells respond to gradients of chemo attractants. They migrate up the gradients and lodge within specific tissue areas. This migration is believed to be of importance in the recruitment of marrow mesenchymal and stromal stem cells to sites of injury and regeneration. This mechanism is less well understood but may be important when these cells are used for repair purposes (16,17).

As mentioned, adult transplanted MSCs may contribute to tissue repair by their paracrine function. This may well be their main mechanism of action as suggested by data from

Table 1 Summary of search strategy

| Items | Specification |
|--------------------------------------|--|
| Date of search | 03/04/2023 |
| Databases and other sources searched | PubMed, Google Scholar, Scopus |
| Search terms | “female stress incontinence”, “homing factors”, “CXCL12”, “secretome”, “low energy shockwave therapy”, “regenerative electrical stimulation” |
| Time frame | Between 2000 and 2023 |
| Inclusion and exclusion criteria | Inclusion criteria: (I) peer-reviewed original articles; (II) reviews covering the field Exclusion criteria: none |
| Selection process | References were independently selected by the authors and included after consensus |

animal models using animal MSCs transplanted into the urethra. These studies showed that *in vivo* differentiation of the MSC into terminally differentiated muscle cells was less important than repair through secretion of trophic factors (9).

MSCs are guided by chemotactic signals such as PDGF α , insulin growth factor and CXCL12 (16). CXCL12 interacts with its receptors CXC chemokine receptor 4 (CXCR4) and atypical chemokine receptor 3 (ACKR3) to exert its physiological and pathophysiological functions (18).

There are studies suggesting that even in the absence of stem cells, the stem cell-derived secretory factors alone may be sufficient to enhance tissue repair after injury. Already in 2003 Askari *et al.* showed that CXCL12 was sufficient to induce therapeutic stem-cell homing to injured myocardium in rats. They suggested that therapeutic strategies focused on stem-cell mobilisation for regeneration (at least of myocardial tissue) must be initiated within days of injury (19). Williams *et al.* (20) showed that in non-human primates (NHPs) with chronic sphincter deficiency, local sphincter administration of CXCL12 without cell therapy, restored short-term urinary sphincter structure and function. The mechanism is still being explored but it is thought to involve an interaction between homing cytokines and their respective receptors on the cell surface of MSCs.

Studies have shown that effects of the sum of secretions from progenitor cells rather than their individual regenerative efficacy stimulate structural and functional regeneration of the urethra (21,22). Cells alone were shown unable to mobilize bone marrow cells and restore vascularization and innervation of the injured NHP sphincter, confirming their limited homing ability. In contrast CXCL12 was effective in restoring sphincter structure and function (20,23). However, there are

reports that seem to contradict these results and question the beneficial effects of CXCL12 on urological tissues (24,25). Thus, Liu *et al.* (24) found in mice that the C-X-C motif chemokine receptor 4 aggravated renal fibrosis, and Macoska *et al.* (25) found that obesity-induced LUT fibrosis and voiding dysfunction in mice could be repressed by antagonizing the activity of the CXCR4 chemokine receptor. These studies focused on inhibition of the secretion of physiologic CXCL12. Ray *et al.* (26) showed that under physiologic conditions CXCL12 forms dimers. Use of low concentrations of monomeric CXCL12, which is the active form stimulating chemotaxis, was suggested by Veldkamp *et al.* (27,28). It cannot be excluded that use of high concentrations of CXCL12 may lead to pathology and malignancy and inhibition of chemotaxis. Both mammalian cells and bacteria secrete monomeric CXCL12 and monomeric CXCL12 is commercially available in recombinant, purified form and currently used for treatment injections. Thus, the way of testing the molecule, the dose and its interaction with other pathways are critical factors for the translation to human use. This is illustrated by one of the few clinical trials where the effects of CXCL12 were assessed. Shishehbor *et al.* (29) investigated the actions of JVS-100, a non-viral DNA plasmid-based therapy that encodes CXCL12 (SDF-10) with an improved longevity. This compound was used as an adjunct to successful revascularization in a Phase 2B randomized, double-blind, placebo-controlled trial. It was found that JVS-100 could not impact wound healing at 3 months, which was the clinical endpoint parameter.

Despite the good underlying rationale and the positive findings in NHP with sphincter insufficiency, studies on the effects of monomeric CXCL12 in human stress incontinence caused by sphincter damage have, to the best

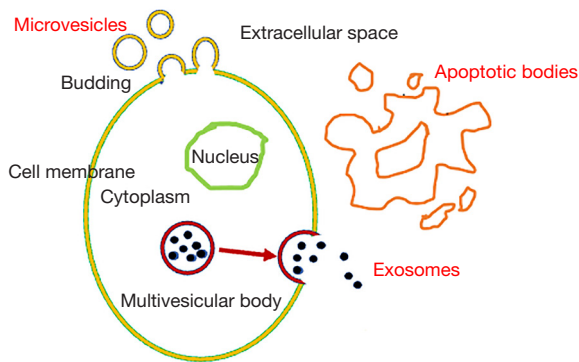


Figure 1 The main classes for biogenesis of extracellular vesicles (redrawn from Hashemi *et al.*, 2022).

of our knowledge, not yet been performed.

Other cytokines have been studied preclinically. It has been shown CCL7 (C-C motif ligand 7) can recruit MSCs to an injured area in the myocardium, where they engraft, produce growth factors, facilitate healing from injury, and improve functional recovery (30). In mice models of simulated birth trauma-induced urinary incontinence, Hijaz *et al.* (31) investigated the expression of CCL7. They found overexpression of urethral CCL7 after vaginal distension but not pudendal nerve transection, suggesting that nerve injury does not contribute to the CCL7 overexpression. In a model of simulated birth trauma-induced SUI in rats, Jiang *et al.* (32,33) combined treatment with CCR1-overexpressing MSCs and CCL7 and found that engraftment of MSCs could increase and promote functional recovery. They suggested that this could be a new therapeutic strategy for SUI.

Secretomes

As mentioned, MSCs home to sites of injury in response to cytokine gradients. A small percentage of the cells may engraft, differentiate, and integrate with host tissues. However, these mechanisms alone cannot explain their therapeutic benefit (9). There is evidence supporting the paracrine hypothesis of stem cell action, postulating that stem cells exert a significant therapeutic effect by secreting the “secretome”, which may exert significant therapeutic effects by their anti-fibrotic, angiogenic, and anti-apoptotic properties (8-10,34). A secretome is defined as all the proteins and secretory pathway constituents secreted by a cell into the extra-cellular space (Figure 1). These secreted factors include microvesicles, exosomes and apoptotic

bodies and can be found in the medium where the stem cells are cultured, also called conditioned medium (CM). The exosomes have an endosome-derived membrane, whereas the microvesicles could directly bud from the plasma membrane, so they have a plasma-derived membrane. The apoptotic bodies are released during the later phase of apoptosis (34). Exosomes are characterized by a diameter of 40–150 nm and a density of 1.09–1.18 g/mL (8), whereas the microvesicles measure 100–500 nm and the apoptotic bodies 500–1,000 nm (34). The secretome of human MSCs can include growth factors, chemokines, cytokines, adhesion molecules, proteases, and receptors.

The molecules within the secretomes may enable more efficient remote communication and targeting than can be obtained with MSCs themselves. The mechanisms involved in e.g., immunomodulation, angiogenesis, inflammation, apoptosis, and tissue repair may be regulated by secretomes (8,9). Conditioned media or exosomes have a potential as a ready-to-go biologic product and may present considerable advantages over cells with respect to manufacturing, storage, handling and product shelf life (8). The use of secretomes, with or without stem cells, may thus represent a promising approach for the treatment of SUI.

Not only exosomes derived from MSCs may be useful. Wang *et al.* (11) evaluated the *in vitro* effects of extracellular vesicles secreted by rat ADSCs in a SUI model and the regulatory mechanism of delivered microRNA-93 (miR-93). ADSCs were isolated and cultured, and extracellular vesicles from the cells were extracted and identified. Their study indicated that miR-93 delivered by ADSCs-extracellular vesicles could regulate extracellular matrix remodeling of SUI fibroblasts and promote activation of SUI satellite cells through targeting F3. However, the authors used male Sprague Dawley animals and the SUI model was not described. Nevertheless, the results illustrate important effects of exosomes.

The effects of exosomes secreted by human urine-derived stem cells injected in and around the pubococcygeal muscle were tested in a rat SUI model produced by balloon dilatation of the vagina (12). They found that after the injection of exosomes there was a significant improvement of urodynamic parameters and a promotion of activation, proliferation and differentiation of muscle satellite cells.

The secretions of MSCs include brain-derived neurotrophic factor (BDNF) which can improve neuroregeneration. BDNF seems to be a key factor in the MSC secretome for the facilitation of functional recovery following a dual simulated childbirth injury (20,33,35). In

female Sprague-Dawley rats, who had undergone bilateral pudendal nerve crush and vaginal distension (injury) or sham injury, Yuan *et al.* (36) showed that BDNF in concentrated conditioned media containing MSC secretome accelerated recovery. BDNF was considered an important contributor, but not the only factor responsible for the recovery of the nerve and muscle injury.

Low intensity shock wave therapy

The possibility of using non-invasive methods to stimulate stem cell growth and mobilization *in vivo* was suggested by recent demonstrations of the effects of low intensity shock wave therapy (Li-ESWT) on stem cells in culture (37-39). Such an approach avoids the requirement for stem cell acquisition, expansion, characterization, transplantation and immune responses of the recipient (40,41). The effects of Li-ESWT are multifactorial and thought to be mediated, at least partly, by upregulation of chemoattractant factors and recruitment/activation of stem/progenitor cells, but also to enhance expression of vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen (24). Studies have shown promising results with Li-ESWT in the management of erectile dysfunction (42-44), where the potential effects on penile tissue have been suggested to include cell proliferation, enhanced cell survival, mitigation of fibrosis and inflammation, and recruitment/activation of endogenous stem cells. This may result in angiogenesis, improved wound healing, and regeneration of muscle and nerve tissue (24). Li-ESWT has been shown to stimulate regeneration of skeletal muscle tissue and accelerate tissue repair processes (41). However, another study showed that Li-ESWT had no incremental effect on PAX7 positive cells and proangiogenic genes *in vivo* (45).

In a single-arm, open-label, multicentre study, Long *et al.* (46) treated 50 female SUI patients with Li-ESWT. They found that 8 weeks of Li-ESWT attenuated SUI symptoms on physical activity, reduced bladder leaks, overactive bladder (OAB) symptoms and significantly improved quality of life.

In a multicenter, single-blind, randomized-controlled trial on sixty female SUI patients, Lin *et al.* (14) evaluated the effects of Li-ESWT. Primary endpoints were the changes in urine leakage as measured by a pad test and validated standardized questionnaires. The secondary endpoint was the changes in a 3-day urinary diary. Four weeks of Li-ESWT significantly decreased urine leakage

based on pad test and validated standardized questionnaire scores, as compared to the sham group. Eight weeks of Li-ESWT significantly reduced urine leakage, increased urine volume and attenuated urgency symptoms. At week eight validated standardized questionnaire scores were significantly improved compared to the baseline. The authors suggested that Li-ESWT could serve as a potentially novel and non-invasive treatment for SUI.

RES

In experimental models of SUI (bilateral pudendal nerve crush and vaginal distension) nerve injury is an important component. This may be the case also in a clinical situation. The evidence for the efficacy of electrical stimulation (ES), daily exercise and their combination in promoting nerve regeneration after peripheral nerve injuries in both animal models and in human patients was reviewed by Gordon *et al.* (47). They concluded that both ES and exercise are promising experimental treatments for peripheral nerve injury that seem to be ready to be translated to clinical use.

Balog *et al.* (48) suggested in a recent review that ES could be a new therapeutic paradigm for SUI treatment. Several preclinical studies have supported this suggestion. In a study on female rats with simulated childbirth injury using a dual-injury model involving both vaginal distension and bilateral pelvic nerve crush, Jiang *et al.* (49) showed that acute electrical stimulation of the pudendal nerve proximal to the crush site upregulated BDNF and βII-tubulin in Onuf's nucleus, which they speculated could be a potential preventive option for SUI after childbirth injury. Jiang *et al.* (50) using the same model found that repeat pudendal nerve stimulation promoted neuromuscular continence, mechanism recovery, again possibly via a BDNF upregulation in the pudendal motoneurons in this model of SUI.

These studies suggested that electrical stimulation of the pudendal nerve may improve recovery after childbirth and ameliorate symptoms of SUI by promoting neuroregeneration after injury. To the best of our knowledge no such RES studies on SUI patients have been performed.

Summary and conclusions

Treatment of SUI with stem cells has been shown to be safe and effective in many patients with SUI (3,5,6). However, since their beneficial effects are mediated by secretion of

factors rather than the cells themselves there is a good rationale for further exploring the therapeutic effects of both homing factors such as CXCL12 and the secretome and/or its components. A large number of human clinical studies are already available on the use of secretome products from MSCs on various conditions (51,52). However, controlled clinical trials on patients with SUI, have to the best of our knowledge, not yet been performed.

Li-ESWT may be a promising alternative and there is good clinical evidence for efficacy. This approach has similar advantages to using cell products like CXCL12 and bypasses the need for expensive and time-consuming cell therapy. RES may be a future alternative for some SUI patients, but so far clinical proof-of-concept studies are lacking.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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