EXPERT VIEW/REVIEW PAPER

Stem Cell Therapy for Pelvic Floor Disorder: A Literature Review of Basic Science to Latest Advancements and Trial Results

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Abstract

Background and aim: Pelvic floor dysfunction (PFD) is linked to pelvic floor muscle dysfunction, which can cause symptoms and anatomical changes. Conservative treatment is the first approach, but surgery may be required if traditional methods fail. However, surgery often results in complications. Stem cell therapies for PFD have been developed to tackle this problem. Therefore, we wanted to review recent studies on stem cell therapies for PFD.

Methods: Comprehensive research was conducted in PubMed, Embase, Cochrane Library, and Google Scholar using specific search terms that included "Stem Cells" and "Pelvic Floor Dysfunction." Only full-text publications in English or Indonesian were included in this review. Pelvic floor dysfunction refers to the changes and anatomical symptoms that arise from impaired function of the pelvic floor muscles.

Review: Stem cells are cells that have unlimited or prolonged self-renewal potential. In recent years, different treatment strategies for PFD using stem cells have been studied *in vivo*. Since PFD can result from muscle function and integrity loss, rebuilding muscle from the cellular level presents an ideal treatment concept. At first, it was believed that transplanted cells would differentiate and bring about functional regeneration. However, current hypotheses suggest that this could be due to direct stem cell transplantation and muscle regeneration, localized agglomeration impacts, trophic effects brought about by the secretion of stem cell growth factors, or immune modulation leading to improved tissue healing.

Summary: Pelvic floor dysfunction refers to the physical symptoms and changes due to a weakened pelvic floor. Scientists have studied various therapeutic techniques involving stem cells to address PFD in living organisms. Stem cells are known for their ability to renew themselves, differentiate into different cell types, secrete growth factors, and modulate the immune system.

Keywords: Conservative treatment, Muscle regeneration, Pelvic floor dysfunction, Stem cell, Stem cell growth factors, Stem cell therapy.

Journal of Obstetric and Gynaecological Practices POGS (2025): 10.5005/jogyp-11012-0036

Introduction

Pelvic floor dysfunction (PFD) encompasses a variety of clinical conditions that can seriously affect a woman's quality of life. Symptoms such as stress urine incontinence (SUI), pelvic organ prolapse (POP), overactive bladder syndrome (OBS), sexual dysfunction (SD), and fecal incontinence are all associated with PFD. Studies have demonstrated that SUI and POP are more prevalent among women in their middle age and beyond. In particular, research indicates that POP affects roughly 30% of middle-aged Chinese women and 19% of middle-aged Australian women while affecting more than 50% of American women over the age of 60.[1] Furthermore, the risk of SUI is 67% greater for women who give birth vaginally as opposed to those who have a cesarean section. By 2050, Wu et al. predict that the number of American women experiencing symptoms of POP would have increased by at least 46%.[2]

The current approach to treating PFD is conservative and focuses on managing symptoms. Surgery is considered the last option for women who have not responded to less invasive treatments.[3] Surgical intervention is a reliable and long-lasting option for PFD, employing synthetic or biological materials to strengthen or support the compromised tissue. Nevertheless, synthetic materials like polypropylene patches have been associated with various complications, including mesh erosion, exposure, pain, and inflammation.[4] The suboptimal mechanical characteristics and rapid degradation of biomaterial meshes have contributed to a diminished ability to achieve anatomical restoration and have imposed limitations on their clinical applicability. Besides, other issues such as infection, bleeding, medical risks, and the potential for injury to neighboring structures may become significant considerations for surgeons and patients.[5]

The dysfunctional structure of the pelvic floor is intrinsically linked to the pathogenesis of PFD. Therefore, without supplementation, a rise in PFD might occur due to any force or action that impairs the integrity of the supporting connective or neuromuscular tissue.

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How to cite this article: Marta KF, Kusuma AANJ, Astawa INM, *et al*. Stem Cell Therapy for Pelvic Floor Disorder: A Literature Review of Basic Science to Latest Advancements and Trial Results. J Obstet Gynaecol Pract POGS 2025;3(1):32–41.

Source of support: Nil

Conflict of interest: None

Fortunately, stem cells can renew themselves, take on different roles, release growth factors, and modulate the immune system. Scientists are exploring how stem cells can be used to treat PFD. Stem cells can differentiate into various tissue cells, including muscle cells and fibroblasts, that comprise the pelvic floor network, compensating for damaged tissue cells when prompted.

Additionally, stem cells may prevent cell death, reduce inflammation, and promote new blood vessel formation. Various stem cell treatments for PFD have been studied *in vivo* in recent years.[6] This article provides an overview of the current state of stem cell therapy for PFD.

Methods

The comprehensive research was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Data sources were searched through several databases, including PubMed, Embase, Cochrane Library, and Google Scholar, to investigate peer-reviewed journal articles and reports on PFD using specific search terms, including "Stem Cells" and "Pelvic floor dysfunction." Moreover, only full-text publications in English or Indonesian were included in this review. We focused on incorporating the latest articles from reputable journals to provide an updated literature review. The primary author independently chose references, and corresponding authors cross-verified them to establish consensus.

Mendeley was used to exclude duplicate articles. This article analyzed 31 contacts. Pelvic floor dysfunction refers to the changes and anatomical symptoms that arise from impaired pelvic floor muscle function. The data-collecting process is shown in Figure 1.

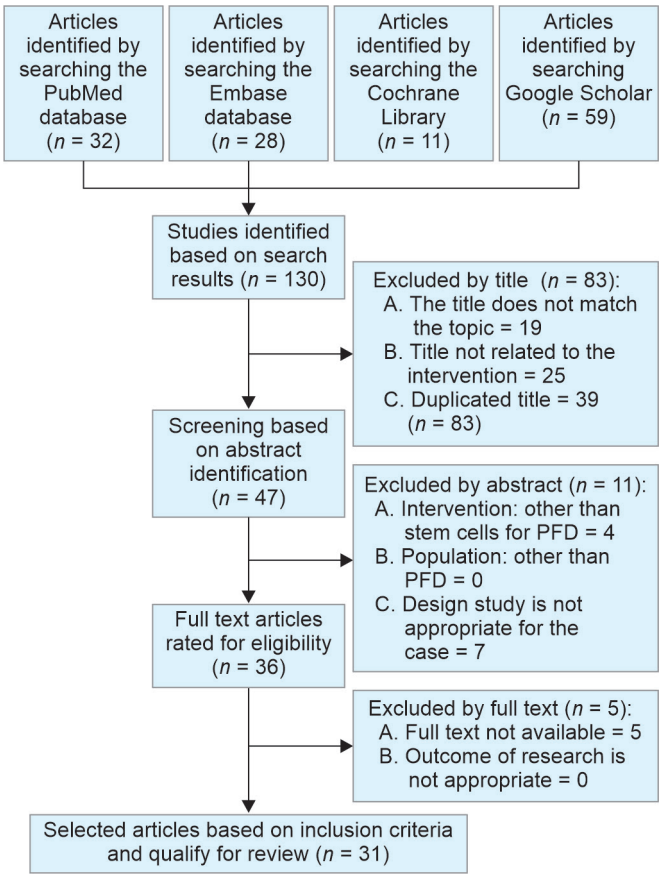


Fig. 1: Data collecting process

Results

Among 130 reports identified, only 31 articles related to the aim of this research were included and analyzed. The selection review process is presented in Figure 1, whereas the overview of the current state of stem cell therapy for PFD is explained later in the section of "Discussion."

Discussion

Pathophysiology of PFD

The term PFD describes the anatomical alterations and symptoms linked to poor pelvic floor muscle activity. Inadequate performance resulting from hypertonicity (higher activity), hypotonicity (lower activity), or improper pelvic floor muscle coordination. Pelvic floor dysfunction encompasses a variety of disorders typically connected to obstetric trauma that are linked to weakening pelvic muscles and tears in the endopelvic fascia. Genital prolapse, stress urine incontinence, and anal incontinence are the most prevalent PFDs. As a result, altered vagina, intestine, lower urinary tract, and SD may be among the related symptoms.[7]

Pelvic floor dysfunction development is intimately related to the functional anatomy of the pelvic floor, where one of its components can be weakened by any external process or force that jeopardizes the integrity of the supporting neuromuscular or connective tissue. The vaginal walls, pelvic connective tissue, and levator ani muscles provide the main structural support for the pelvic floor. Pelvic floor dysfunction could result in pelvic floor problems. Thus, in the absence of sufficient assistance, this could result in a rise in PFD. Pelvic floor dysfunction is primarily caused by the interplay of muscles and connective tissues in the pelvis, which results in a lack of pelvic floor support. Abnormalities in connective tissue and elastin/collagen metabolism primarily characterize this. These anomalies include changes in the overall content and ratio of collagen subtypes, insufficient crosslinking of collagens, and disturbances in elastin homeostasis brought on by aberrant elastin synthesis or degradation. In order to improve pelvic floor function, PFD therapy attempts to strengthen weak pelvic floor tissues and promote tissue remodeling. Research has also revealed that the endopelvic connective tissue of women with vaginal prolapse has a unique extracellular matrix architecture and lower collagen concentrations.[8]

One of the most important elements of the connective tissue's extracellular matrix is collagen, which keeps the pelvic floor's supporting roles intact. The main fiber in the extracellular matrix that resists tensile forces, such as stretching, is collagen. Under stress and damage, the collagen that makes up connective tissue undergoes remodeling.[9]

Collagen makes up around 80% of the weight of the ligaments in the hip and extremities; hence, it is extensively used in these structures. As the main fiber in the extracellular matrix, collagen provides vital defense against tensile forces such as stretching. The collagen that makes up connective tissue remodels in reaction to damage and stress.[10,11]

Muscle atrophy and dysfunction can lead to PFD, which emphasizes the significance of regaining cellular muscle integrity and function. Research on humans and animals has produced successful functioning results.[12–22] Theories explaining stem cells' modes of action have been developed as a result of ongoing study.

The pelvic floor support structures are schematically depicted in Figure 2, together with the neurological control system that includes the brainstem, spinal cord, cortical, and peripheral nerve components for the levator ani muscles. As seen in Figure 3A, under normal circumstances, the levator ani muscles keep the pelvic floor closed, providing a lifting restriction to prevent the pelvic floor from falling. The pelvis is effectively an isobaric chamber in this situation because the weights in the front and rear compartments are broken even with and adjusted, balancing each other out. The pelvic organs can slip, and the levator rest can be forced open when the muscles are damaged or weak (Fig. 3B). One or both of the vaginal partitions will slip in this situation. The weight difference between the stomach weight and the barometrical weight is caused by the ensuing misalignment (Fig. 3C). The tissues that join the uterus and vagina to the pelvic dividers are subjected to exceptional tensions as a result of this weight's action on the vaginal dividers. The pelvic organ return is determined by the interplay between connective tissue connections and muscle activity in this process.[23]

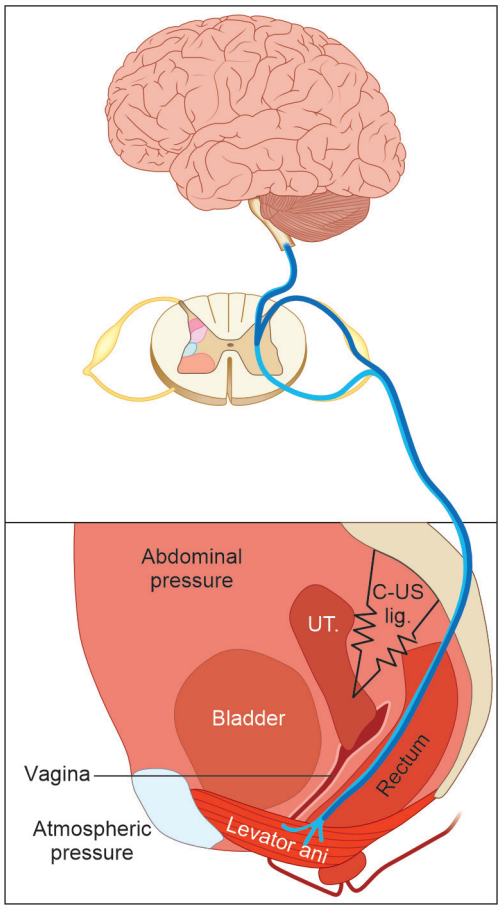
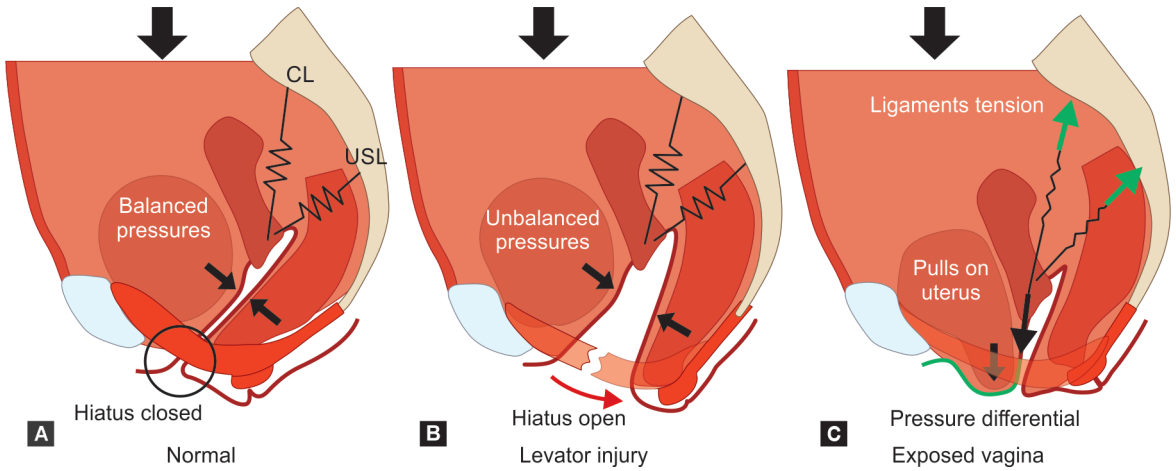


Fig. 2: Simplified schematic of the pelvic floor support structures
Source: DeLancey. Pelvic floor anatomy and pathology. Elsevier 2019.

Introduction of Stem Cells in PFD

The use of stem cells in contemporary regenerative medicine began in the 1950s, with the first bone marrow transplant performed in 1956. Stem cells are undifferentiated cells with a protracted capacity for regeneration without appreciably altering their basic characteristics.[6] In specific physiological or experimental conditions, they can differentiate into a variety of specialized cell types. Pluripotent stem cells are known as mesenchymal stem cells or MSCs. Mesoderm-derived MSCs are an adult nonhematopoietic stem cell type. They can self-renew and develop into ectodermic and endodermic cells, as well as mesoderm lineages, including chondrocytes, osteocytes, and adipocytes. Many tissues and organs, including bone marrow, adipose tissue, placental tissue, amniotic fluid, umbilical cord vein, Wharton's jelly, and endometrial, can be used to produce MSCs.[12] However, regarding the limited data on randomized trials of stem cell therapy in PFD, we only reviewed two types of MSCs in this article: Adipose-derived stem cells (ADSCs) and autologous muscle-derived cells (AMDC).

Stem cells are defined as cells with unlimited or prolonged self-renewal potential and the ability to produce at least one differentiated mature cell type. Each cell has a specific span of life, which will end with death and be replaced by new cells. This event is known as regeneration. The ability to regenerate each cell differs depending on the type and type of cell itself. Cells with the most substantial potential for regeneration are stem cells,



Figs 3A to C: Schematic representation of the interaction between the levator ani muscles, prolapse of the anterior vaginal wall, and suspension of the proximal/sacral uterine ligaments
Source: DeLancey. Pelvic floor anatomy and pathology. Elsevier 2019.

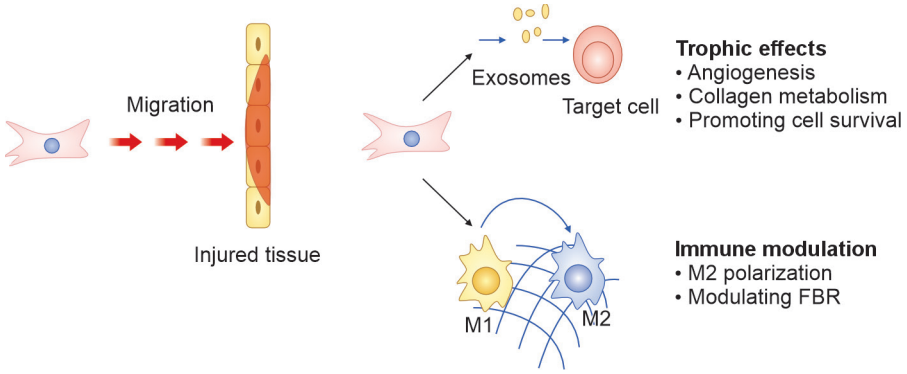


Fig. 4: Simplified representation of the potential roles of stem cells in treating PFD. FBR, foreign body response

Source: Sima et al. MSC-based therapy in female pelvic floor disorders. Cell Biosci 2020.

whereas cells with lost potential are mature cells. The potential for cell regeneration will decrease and disappear along with maturity.[7]

Initially, there was hope that transplanted cells might develop into fully functioning new tissue. Some of the tools proposed include muscle regeneration after stem cell transplantation, the effects of local aggregation, the trophic impacts of secreted stem cell growth factors, and immunological regulation leading to enhanced tissue recovery.[11]

Physiology of Stem Cells for PFD

Migration to the Site of Injury

Recent studies have shown that specific stem cells, often called "homing" cells, can migrate to damaged areas and establish permanent residency there. These stem cells can pass through the endothelium of vascular tissues and find their way to the appropriate location. However, it remains unclear whether stem cells actively adhere to tissues through cell adhesion and transmigration processes like leukocytes or whether they are stuck in small blood vessels. Although stem cells produce various cell adhesion molecules and receptors, including chemokine and integrin receptors, much is still unknown about stem cell migration and homing.[12]

Currently, injecting stem cells through the periurethral is the conventional stem cell therapy for PFD.[4] It is still difficult to precisely target stem cells at the site of injury. The homing ability of stem cells is critical to the efficacy of PFD treatment because of the significant damage to the pelvic floor's connective tissue. Stem cell infusion intravenously may offer a successful cell-based treatment option. Cruz et al. showed that after creating labor injury in a mouse model, stem cells were distributed to the pelvic organs.[13] Ben Menachem-Zidon et al. investigated the effects of systemic and local injections of stem cells on binding, survival, differentiation, and angiogenesis using a mouse model of vaginal injury.[18] Their findings indicated that while both transplantation methods promote host angiogenesis, binding was less efficient with local transplantation at all time points compared with systemic administration. This suggests that stem cells transplanted systemically enhance tissue repair by targeting the injury site more effectively.[15]

Paracrine Effects

At first, it was thought that stem cells' capacity to differentiate and replace cells was what gave them their therapeutic effects. On the other hand, new research indicates that transplanted stem cells only have a brief lifespan in the body. Nowadays, it is thought that paracrine actions—which include exosome synthesis or the secretion of trophic and immunomodulatory factors—are what gives stem cells their therapeutic effects. These effects can improve tissue repair and manifest in the initial days following stem cell injection. In regenerative medicine, acellular therapies employing stem cell secretions are gaining popularity. Trophic effects and immunological modulation are two of the paracrine effects of stem cells in the treatment of PFD (Fig. 4).[15]

The term "stem cell secretion" describes the way in which stem cells release different chemicals, such as chemokines, cytokines, and exosomes. With the focus shifting from stem cell differentiation to the therapeutic impacts of stem cells, a lot of research has focused on using stem cell secretion to treat a variety of illnesses. Stem cell-based acellular therapy offers therapeutic benefits without the risk and complexity of live cell transplantation, making it a more scalable and dependable method.[16–21] Using concentrated conditioned media from stem cells or exosomes produced from stem cells, numerous attempts have been undertaken to look into the potential therapeutic impact of stem cell secretion on PFD.[22]

Liu et al. performed an *in vivo* study to assess collagen metabolism in fibroblast cultures from postmenopausal women with and without SUI after introducing exosomes made from human stem cells. Transmission electron microscopy and western blotting were used to confirm that exosomes were prepared using ultracentrifugation of the stem cell-conditioned media. After 6 hours of culture, exosome-treated vaginal fibroblasts expressed more type I collagen, TIMP-1, and TIMP-3 but less MMP-1 and MMP-2. In vaginal fibroblasts from women with SUI, exosomes increase type I collagen content, as evidenced by an increase in collagen formation and a decrease in collagen breakdown.[24]

In a different study, Ni et al. examined the *in vivo* and *in vitro* therapeutic potential of human ADSC-derived exosomes in SUI. Similar techniques are used in Liu's work to isolate and describe exosomes.[24,25] Female rats and mice were given peripheral injections of ADSC or ADSC-derived exosomes to generate the SUI model. Following this, the pudendal nerve was transected (TPNs), and vaginal distension (VD) was performed. *In vitro* research has shown that exosomes stimulated the growth of Schwann cell lines and skeletal muscle in a dose-dependent way. *In vivo* testing revealed that mice treated with exosomes had more striated muscle fibers and peripheral nerve fibers inside the urethra, as well as improved bladder capacity and LPP. The authors' proteomic analysis showed that many proteins involved in brain and skeletal muscle

regeneration were present in ADSC-derived exosomes. However, the underlying mechanisms are yet unknown.[25]

In a mouse model, stem cell-derived exosomes were demonstrated to have a therapeutic effect on SUI. This effect was linked to the phosphorylation of extracellular regulated protein kinase in satellite cells, which is necessary for the regeneration of skeletal muscle. The muscle in the pubococcygeus showed nearly normal fibrosis and muscle form eight weeks after the exosome injection. Furthermore, the injection of exosomes raises the phosphorylation of ERK, which facilitates the activation, proliferation, and differentiation of satellite cells. However, the myogenic effect of exosomes is nearly neutralized by extracellularly regulated protein kinase inhibitors.[11]

Promotion of Cell Survival or Trophic Effects

Within mesenchymal tissues, worn-out cells can be replaced with MSCs. Furthermore, MSCs do not require the induction of new mesenchymal phenotypes in order to have trophic effects on adjacent cells. This implies that they can affect tissue or cell regeneration only when bioactive substances are involved. Stem cells are remarkably capable of secreting extracellular matrix, cytokines, and growth factors—all essential for maintaining cell viability. Together, these secretions facilitate the repair of injured cells, lessen the extent of tissue damage, and hasten the healing process. In addition, stem cells function as vascular pericytes, strengthening the integrity of the endothelial cells lining blood arteries and reticular cells and supporting the preservation of the hematopoietic stem cell niche.[11] Adult stem cells have recently been used in animal models of stress urine incontinence, anal incontinence, and vaginal prolapse to initiate tissue regeneration. By fusing stem cells with the existing muscle structure and releasing different trophic factors, like interleukins and growth factors, it was believed that the stem cells would promote the regeneration of muscle and nerve tissues. Numerous vital cellular functions, including adhesion, migration, differentiation, proliferation, and death, are regulated by these factors.[12]

During stem cell-based therapy for PFD, tissue regeneration is greatly aided by the paracrine activities of stem cells. They improve the survival of muscle cells, promote host angiogenesis, and control the metabolism of collagen, which is frequently disturbed in POP's connective tissue. Stem cells have the potential to regulate collagen metabolism through paracrine activities, hence improving the functional characteristics of fibroblasts. Exosomes have been shown in preclinical studies to increase the synthesis of collagen I and III during the initial phases of wound healing. However, in the later phases, they inhibit the expression of collagen, which lessens the creation of scars. However, it has been demonstrated that stem cells prevent TGF-induced myofibroblast growth and collagen deposition in organ fibrosis. They thus represent a viable new treatment option for fibrotic diseases.[12]

Immune Modulation

The scientific community is becoming more and more interested in the effects of stem cells on the immune system. According to preliminary research, stem cells do not promote the development of alloreactive lymphocytes, which implies that they might have immunological benefits.[15] Nevertheless, studies have indicated that immunological rejection may cause allogeneic stem cell transplantation to fail. Ankrum et al. conduct a thorough examination of stem cell immunogenicity in their review, concluding that "stem cells are immune resistant and lack immune privilege."[16] The context of exposure to inflammatory stimuli is a crucial component in determining the immunogenic and immunosuppressive characteristics of stem cells. Stem cell-based therapies have been used to treat autoimmune diseases, sepsis, and graft-vs-host disease (GVHD) because of their varied immunomodulatory properties. Through the reduction of T and B lymphocyte activation and proliferation, the suppression of dendritic cell maturation, the inhibition of natural killer cell proliferation and cytotoxicity, the promotion of M2 macrophage polarization, and the increase in regulatory T cell numbers, stem cells can modulate both the innate and adaptive immune systems. This process is driven by the paracrine effects of stem cells that produce cytokines, including TGF-, PGE2, IL-6, and IL-10.[16]

Because of the immunomodulatory qualities of stem cells, their use in conjunction with biomaterials for the treatment of POP has demonstrated encouraging results in modifying the foreign body response (FBR). Since the FBR is the last stage of the inflammatory and wound-healing processes after medical implantation, it ultimately decides whether the implanted biomaterial is accepted or incorporated. It has long been thought that excessive FBR, which exposes or erodes the synthetic polypropylene mesh used in POP pelvic floor reconstruction surgery, is the source of the mesh's degradation. However, recent studies in animal models have shown that stem cells may decrease FBR and increase the biocompatibility of meshes through interactions with immune cells, including macrophages. This shows that patients with POP may experience fewer postoperative complications as a result of stem cells' capacity to modify the immune system.[15]

Preclinical Studies of MSCs-based Therapy for PFD

Mesenchymal stem cells, the cells used in regenerative medicine the most frequently at this time, have been studied extensively for PFD due to their easy absorption, pleiotropic effects, and plentiful supplies. According to preclinical research, MSCs can be administered as MSCs, MSC secretions, or MSC aggregate networks to stimulate tissue regeneration and influence the immune response successfully. Current research has shown that MSCs function by secreting several types of bioactive compounds that promote target cell activity and boost immune responses; however, the precise mechanisms underlying the therapeutic effects are yet unknown. Furthermore, cell-free therapy is currently thought to be a feasible strategy for PFD since MSC-derived extracellular vesicles like exosomes are swiftly turning into essential tools for tissue regeneration and repair. Animal models have demonstrated its therapeutic efficacy, and extensive research has been done on the safety concerns related to cell transplantation. To date, not many clinical trials have been carried out to verify if cell-free therapy is beneficial for PFD patients.[15,16]

Stress Urinary Incontinence

Extensive preclinical research is currently exploring the potential of stem cells as a treatment option for PFD, utilizing diverse animal models, cell sources, administration techniques, and response evaluation systems. Of the various potential treatments for SUI, stem cell transplantation has been the focus of extensive investigation.[17]

A growing body of evidence suggests that stem cell transplantation could be a viable cure for urinary incontinence, as it can repair damaged structures and functions within the urinary

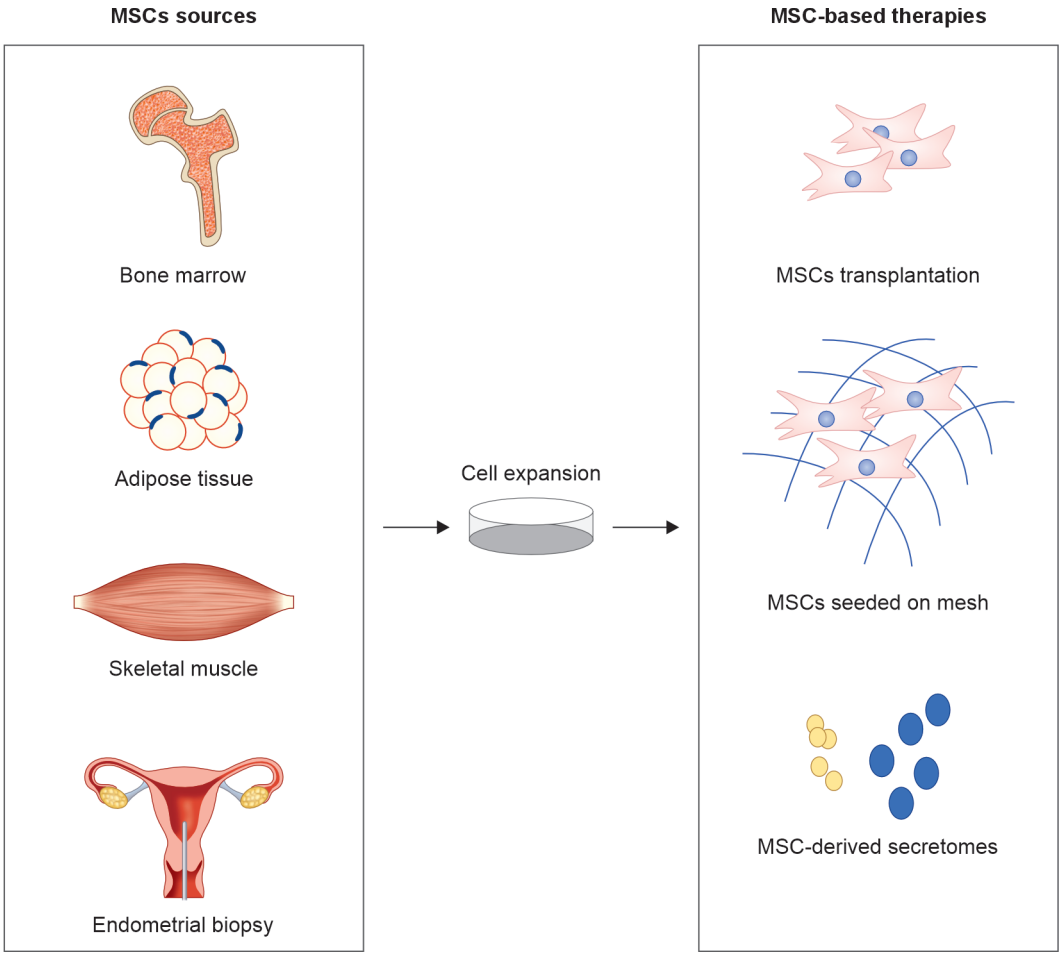


Fig. 5: Schematic representation of the different stem cell sources and stem cell-based therapies for PFD

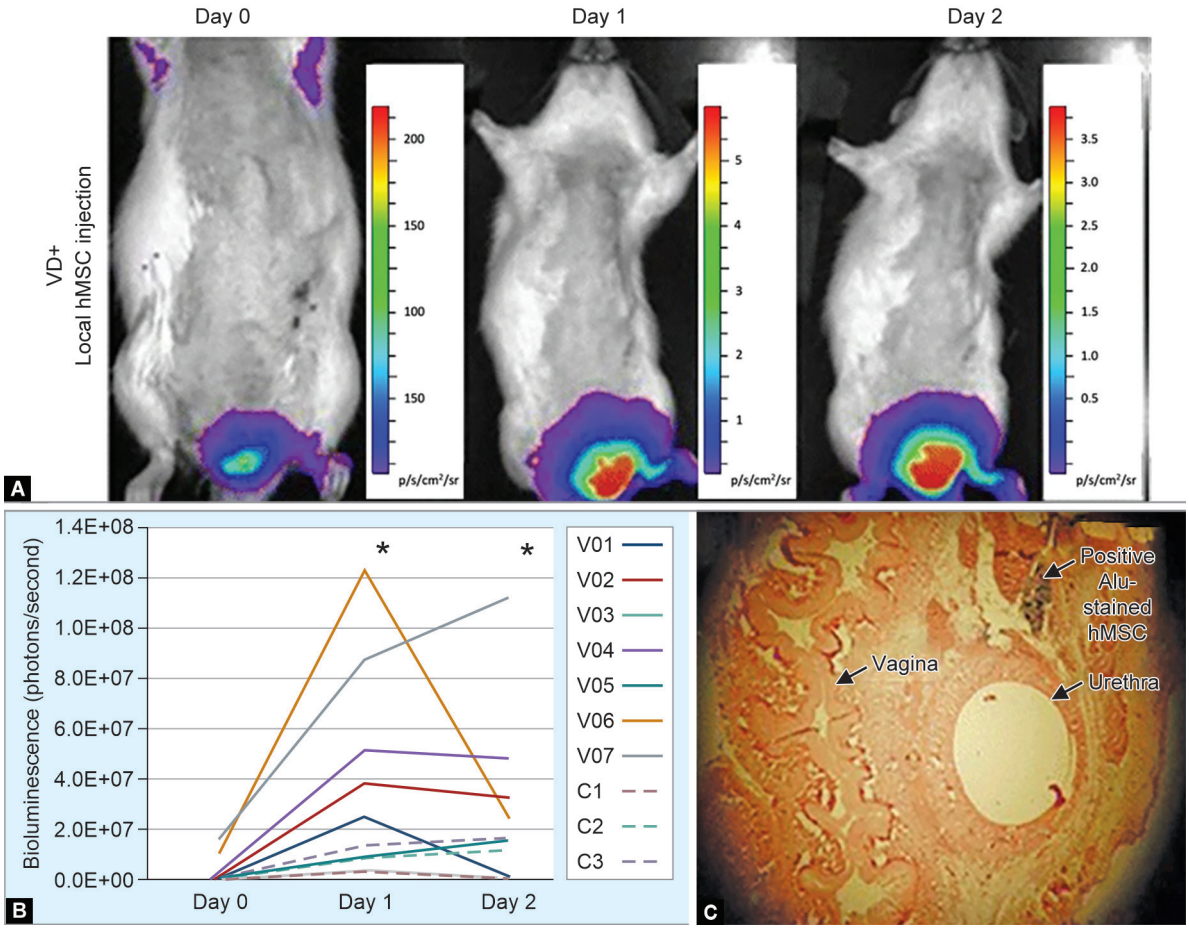
Source: Sima et al. MSC-based therapy in female pelvic floor disorders. Cell Biosci 2020.

system. Nevertheless, the time stem cells remain in their injection site remains a topic of debate, as different studies have reported varying survival estimates.[10] However, further research is needed to evaluate the findings as there was no detailed data on limited lifespan and survival estimates, even though these findings are essential proof in the treatment of PFD (Fig. 5).

Stem cell distribution in the pelvic organs after intravenous injection in mice with VD was observed by Cruz et al. Transfected stem cells continuously produced green fluorescence protein (GFP) after transfection, allowing for fluorescence imaging analysis.[13] Both 4- and 10-days post-VD, GFP+ MSCs were seen in the pelvic area using *in vivo* imaging; however, overall flow reduced with time. Human stem cells have been studied for their potential to help with urine incontinence, and their destiny after injection has been investigated in several studies. Several methods were used to detect transplanted stem cells: *in situ* hybridization for tracking of digoxigenin-labeled DNA probes that repeat the human Alu genome and *in vivo* bioluminescence imaging (BLI) for real-time assessment of stem cell viability and distribution following local periurethral injection. The BLI signal improved in VD mice 1 and 2 days after stem cell injection. Still, non-VD animals showed no such improvement (Fig. 6). These results imply that stem cells injected intravenously travel to the site of damage, providing a viable cell-based therapeutic pathway for treating SUI. However, stem cells do not stimulate tissue regeneration via differentiation and replacement due to their fast loss.[11]

Furthermore, Figure 6 shows the results of a study involving periurethral injection of luciferase-expressing human mesenchymal stem cells (hMSCs) in animals with VD. Bioluminescence imaging revealed an increased signal in animals with VD on days 1 and 2, indicating hMSC recruitment/viability. The presence of hMSCs in the urethra was confirmed using human-specific Alu repeats, but no positive signal was observed after the BLI signal disappeared. No discernible variations were noted in mice without VD.[11]

A vaginal incision was made in a mouse model to create vaginal injury, and the survival, differentiation, and angiogenic effects of transplanted stem cells were evaluated by Ben Menachem-Zidon et al.[18] Based on their findings, the authors suggest that transplanted cells can develop an endothelial phenotype and be detected in capillary-like structures. Interestingly, cells labeled with green fluorescent protein (GFP) were observed to migrate to areas of vaginal damage and persist for a minimum of 30 days.[23,26–32] The authors posit that the transplanted stem cells do not merge with the host endothelial cells but instead undergo *in situ* differentiation to transform into endothelial cells. The authors could not elaborate on why endothelial phenotypes and long-term presence were detected exclusively in animals that had received systemic rather than local stem cell transplants.[16]



Figs 6A to C: BLI of hMSC localization in VD rats

Source: Sima et al. MSC-based therapy in female pelvic floor disorders. Cell Biosci 2020.

Fecal Incontinence

Research into stem cell transplantation for fecal incontinence has occurred concurrently with studies on urinary incontinence. Salcedo et al. study discovered that mesenchymal stem cells (MSCs) enhanced anal sphincter function in mice with sphincterotomy-induced anal incontinence, with anal sphincter pressure evaluated 10 days post-damage.[19] They then compared anal sphincter pressure before and after intramuscular and serial intravascular stem cell injections to examine the regenerative impact of stem cells on anal sphincter injuries. Both the intramuscular and intravascular groups saw an increase in anal sphincter pressure that persisted for 5 weeks. The intravascular injection group also showed the most minor scarring of the two stem cell treatment groups, but both showed increased collagen deposition. Similar findings of increased anal sphincter pressure after stem cell administration were reported by Kuismanen et al. in the same animal model. Because of its biocompatibility and ability to integrate into tissues with minimal FBR, the polyacrylamide hydrogel Bulkamid was also proven to be an effective transporter for stem cells.[20]

Pelvic Organ Prolapse

Numerous scientific investigations have been carried out on stem cell-based POP therapies. The elastic modulus was considerably higher in the MSC group, according to research by Zhang et al. using the rhesus macaque (mice) model, suggesting that the vaginal tissue injected with MSCs was stiffer than the vaginal tissue lacking MSCs.[33] Additionally, MSCs were shown to increase elastic modulus in the treatment of SUI in a rat model by Zou et al.[34] Furthermore, variations in ECM deposition and smooth muscle regeneration can account for the variations in biomechanical parameters following MSC injection in those investigations.[33]

Preclinical Studies of ADSC-based Therapy for PFD

In many preclinical studies, stem cell transplantation is a potential therapeutic strategy for urinary and fecal incontinence. Lin et al. initially disclosed mouse model research using autologous ADSCs to treat SUI. Bilateral ovariectomy and postpartum vaginal balloon dilation in mice caused aberrant voiding.[18] To simulate menopause in mice, a bilateral ovariectomy was performed, utilizing ADSC isolated from peri-ovarian fat from rats instead of the more commonly used subcutaneous fat. The ADSC was then administered either via injection into the urethra of mice or intravenously through the tail vein. After 4 weeks, conscious cystometry revealed that 80% of the control rats experienced micturition impairment, while only 33% of the ADSC-treated mice did. ADSC-treated normal voiding mice showed significantly greater smooth muscle and elastin content than controls and aberrant voiding animals. These findings support the theory that transplanted ADSCs can restore urethral function and that migrating ADSCs toward the wounded urethra could help alleviate voiding dysfunction. This study reveals that stem cells that

have been tagged can still be detected in the body's connective tissue up to 4 weeks after donation. However, subsequent research has uncovered that while stem cells profoundly impact tissue regeneration, they possess a limited lifespan.[18]

Stem Cell-based Tissue Engineering for PFD

Numerous studies have explored the potential of tissue engineering treatments, particularly in treating POP (as illustrated in Fig. 5). These treatments involve combining stem cells with cutting-edge materials or tissue. In cases where autologous tissue is lacking or damaged, mesh implantation can help alleviate symptoms and improve long-term outcomes. Recent research has shown that combining stem cells with meshes can produce even more promising results, as the mesh acts as a scaffold for cellular attachment and provides essential mechanical and structural support for pelvic tissues. Meanwhile, stem cells' immunomodulatory and anti-inflammatory characteristics may help rein in high FBR. As a result, tissue engineering is an emerging subject in pelvic floor restoration since it may be used to reinforce soft tissues.[21]

Stem cells have shown remarkable modulatory characteristics for extracellular matrix remodeling and inflammatory responses, and their use in tissue engineering treatment for pelvic floor restoration has gained popularity in recent years, while the underlying processes remain elusive. The immunomodulatory impact of eMSC on macrophage reactions to a novel mesh type—polyamide knitted mesh covered in stabilized gelatin—was examined in this study using an abdominal subcutaneous wound repair model. Angiogenesis, neotissue formation, and wound healing were all enhanced by the paracrine action of human eMSCs. The mesh's biocompatibility was enhanced by seeding it with eMSC, which decreased chronic inflammation and increased the deposition of crimped physiological collagen around mesh filaments. Over time, this decreased the mesh-tissue complex's stiffness.

Clinical Trials of Stem Cell-based Therapy for PFD

As a result of encouraging outcomes observed in animal models, several clinical trials, phases I until II, are presently exploring the effectiveness of stem cell transplantation therapy for PFD. While SUI and fecal incontinence stem cell treatments, have only been the subject of a few minor clinical studies, Phase I and II clinical trials have typically involved restricted participants.[12] Furthermore, the clinical trials of stem cell-based therapy for PFD are summarized in Table 1.

Table 1: Clinical studies summary of stem cell-based therapy for PFD

No.	*Author (Year)*	*Methods*	*Type of stem cells*	*Results*
Autologous muscle-derived cells (AMDC)				
1	Sebe et al. (2011)	Prospective study	Autologous muscle-derived cells (AMDC)	Autologous muscle-derived cells (AMDC) for treating SUI are safe and effective in clinical studies. Skeletal muscle marker expression helped researchers determine that the AMDC employed in this study was a hybrid of fibroblasts and myogenic cells. Intrasphincteric injection of AMDC in women with severe SUI was studied in this research for its effectiveness and safety. There were no serious adverse effects. However, urine culture results indicated that three people had a UTI.[25]
2	Majka et al. (2014)	Randomized trial (Phase I)	AMDC	Stress test assessment and questionnaire scores indicated a 75% success rate for AMDC in SUI patients for 2 years.[26]
3	Carr et al. (2013)	Prospective study	AMDC	According to results reported by Majka et al., this research then assessed these patients 2 and 4 years after cell treatment using a validated questionnaire. It was found that autologous cell therapy had greatly improved patients' quality of life and psychiatric disorders. Patients with greater AMDC doses in their intrasphincteric injections had better clinical results. Therefore, this research could determine that this was the ideal cell dosage for cell treatment.[27]
4	Peters et al. (2014)	Prospective trial	AMDC	Tested a larger sample using the same cell isolation process and urine incontinence assessment, and they found that four cell dosages were both efficacious and well tolerated by individuals with SUI.[28]
5	Frudinger et al. (2018)	Single-center, explorative, baseline-controlled clinical trial	AMDC	In 39 patients (34 females and 5 males), AMDC was injected AMDC into the external anal sphincter and reported a significant decrease in the number of incontinence events per week, with a corresponding increase in patient satisfaction. Despite favorable symptomatic findings, anorectal manometry and ultrasonography showed no physiological alterations.[30]
Adipose-derived stem cells (ADSCs)				
1	Arjmand et al. (2021)	Systematic review	Adipose-derived stem cells (ADSCs)	One year after receiving an injection of ADSC with collagen gel, 3 out of 5 patients presented a negative cough test, and the questionnaire demonstrated subjective improvement in all patients. Ten patients had ADSC transplanted into the periurethral area, and the short-term findings were given. No problems were recorded despite the dramatic rise in urinary incontinence, and just one patient had mild difficulty voiding.[29]
2	Sarveazad et al. (2017)	Randomized trial	ADSC	There was no significant change when comparing the cell group with the control group on the Wexner score, an indicator of muscular function. Increased muscle tissue was seen using endorectal sonography and electromyography at the repair site, but this finding was not corroborated via biopsy or magnetic resonance imaging.[31]

A randomized, double-masked, placebo-controlled clinical trial was conducted in 2018 to evaluate the efficacy and safety of AMDC in women with SUI. The study considered a range of important metrics for success, including stress incontinence events, pad tests conducted over 24 hours at home and work, and the Incontinence Quality of Life Scale (IQOL). At 12 months, there was no significant difference between the placebo and AMDC groups in the proportion of patients who met the combined end goal of at least a 50% decrease in the frequency of episodes of stress incontinence, a 24-hour pad weight test, or an in-office weight test relative to baseline. The responder rate was lower in the placebo group than in the AMDC group. Still, the difference was not statistically significant when using more stringent endpoints, such as at least a 75% reduction in the frequency of stress incontinence episodes or, at most, 1 episode of stress incontinence reported over 3 days. Furthermore, according to the rigorous end goal, participants who demonstrated a response to treatment had a more significant rise in mean IQOL score compared with those who did not. The study confirmed the validity of stress incontinence frequency events as a clinically significant end goal. This goal can be employed in future trials to assess efficacy by examining the relationship between reduced episode frequency and enhanced IQOL scores. In conclusion, this clinical trial is the largest clinical study looking into cell therapy for SUI, and it demonstrates that AMDC transplantation is an acceptable treatment for SUI, even though the evaluable sample size was decreased because of an unexpectedly high placebo response rate. The pervasive existence of the placebo effect complicates clinical research evaluating the efficacy of cell treatment. Notwithstanding these limitations, the research provides a useful framework for planning future cell therapy studies for SUI.[22]

For individuals with SUI, the use of stem cells looks to be a workable and safe technique with therapeutic benefits. However, a consistent approach to stem cell-based treatment in SUI is currently being researched due to variability in preclinical and clinical studies. It is unknown why cell therapy is not more effective in treating SUI patients. However, subpar accuracy in cell administration may be to blame. Female goats were used in a preclinical investigation to evaluate the precision of injections via the transurethral and periurethral routes. Regardless of the injection technique, only a tiny percentage of the cell depot is delivered to the external urethral sphincter.[12]

The current clinical trials have not fully confirmed the efficacy and safety of stem cell transplantation. Still, they have established it as a promising alternative therapy for urinary and fecal incontinence by enhancing the function of the urethral or anal sphincters. Although this research only used a small sample size, its information helps us to understand how stem cells might be used to treat illness. More extensive clinical studies of stem cell-based therapy for PFD are needed, ideally with more significant sample numbers, integrated stem cell treatment modalities, and the inclusion of a placebo control group.[22]

Challenges and Future Prospects

Autologous stem cell research in PFD treatment has been limited by a need for more information on the most appropriate cell type, cell dose, and cell injection technique. Moreover, the destiny of implanted cells is difficult to follow in human trials, making this method less ideal than animal investigations. This highlights the need to identify reliable methods for detecting stem cell distribution, proliferation, and differentiation in human individuals *in vivo*. The treatment effectiveness is also lower than anticipated in clinical studies. Some patients are excused from therapeutic obligations.

Several *in vivo* stem cell-based therapies for PFD have been explored in recent years. Stem cell therapy has potential benefits, but concerns remain about its safety. While stem cell transplantation has proved safe and efficient in most mouse models, there needs to be more research on its long-term impacts. Its dose-effect profile was assessed in a sphincter-detached canine model to evaluate the safety of skeletal muscle precursor cell therapy. No harmful effects were detected based on histological pathology, blood cell count, or liver and kidney function indicators up to 9 months following cell injection at a rate of 25–100 million cells per milliliter. This time frame is comparable to observing humans for two to three years.[15]

However, there currently needs to be a definitive animal model for PFD, and animal models that only imperfectly replicate illness causes or symptoms are thus inadequate. Therefore, future studies should use an increasing number of superior animal models. All of the preclinical experiments employed periurethral injection as the transplantation technique, whereas many researches used intravenous injection to categorize the migratory capabilities of stem cells and compare the two injection methods. It is also worth noting that various research findings on how long implanted stem cells live and their ability to differentiate *in vivo* have needed to be more consistent.[22] Due to persistent challenges, a clinical-scale method for purifying or enriching the required cells from a differentiated population of human.

Conclusion

Although there has been significant progress in implementing cell-mediated therapies for treating PFD, several crucial aspects still require further investigation and improvement. Improving the survival and metabolism of the injected cells is necessary to enhance the quality of bioengineered tissues. Additionally, non-invasive tracking of implanted cells' long-term viability and functionality is critical, and finding a tool to monitor cell fate would be a breakthrough. Finally, alternative approaches such as regenerative pharmacology must be further developed as stand-alone or combined treatment strategies for patients with PFD. In conclusion, the potential for stem cell therapies in combination with regenerative pharmacology for treating patients with PFD is enormous. Overall, stem cell-based treatment for PFD has shown promising results in small animal models. Sphincter damage and VD were the most common causes of deformity in the mouse animal model used in this investigation.

In contrast, pudendal nerve injury and vaginal incisions occurred less often. The inconsistency in these studies' results may be explained by the fact that even little variations in cell sources, culture conditions, and cell dosages can profoundly impact the injected stem cells' ability to function and the therapy's efficacy. Therefore, future research should establish universal procedures for stem cell-based treatment for PFD.

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