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EFFICACY AND SAFETY OF CELL-BASED THERAPIES FOR STRESS URINARY INCONTINENCE: A SYSTEMATIC REVIEW

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Abstract

This review article investigates the efficacy and safety of cell-based therapies in treating stress urinary incontinence (SUI), which significantly impacts the quality of life for millions of women globally. With a prevalence rate of 10%–40%, SUI often results from anatomical defects such as hypermobile urethra and intrinsic sphincter deficiency. Traditional conservative treatments, including behavioral therapy and pelvic floor exercises, may offer initial relief, but invasive surgical interventions carry potential complications and varying success rates. Emerging evidence highlights the promise of stem cell therapy, particularly utilizing muscle-derived stem cells (MDSCs) and adipose-derived stem cells (ADSCs), in regenerating urinary sphincter function. Preclinical and clinical trials indicate substantial improvement in incontinence scores, sphincter contractility, and overall quality of life following autologous stem cell injections, with reported cure rates ranging from 59% to 90.5%. Importantly, these interventions demonstrated favorable safety profiles with minimal adverse effects. This review consolidates existing literature on cell-based therapies for SUI, underscoring their potential as a transformative approach in the management of this condition. Future studies and controlled trials are necessary to further elucidate their long-term outcomes and optimize treatment protocols.

Keywords: Stress urinary incontinence, stem cell, clinical trials, stem cell therapy, stem cell transplantation, regenerative medicine, cell-based therapy.

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Introduction

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

Stress urinary incontinence (SUI) can result from anatomical incontinence, often referred to as hypermobile urethra and intrinsic sphincter deficiency (ISD). The conservative management of female SUI includes behavioral therapy, biofeedback, and pelvic floor muscle training. These interventions are typically straightforward, cost-effective, and associated with a low chance of side effects, allowing for other potential treatments in the future if needed [3]. When conservative strategies prove ineffective, more invasive options such as mid-urethral sling implantation, bulking agent injections, and Burch colposuspension may be considered. Surgical options offer effective treatment for SUI but carry a risk of complications. The mid-urethral sling is advantageous due to its reduced intervention time. Nevertheless, various organizations have consistently cautioned against the use of mesh materials in treating female urinary incontinence because of numerous serious adverse events associated with them. The placement of an artificial urinary sphincter is suggested for women with moderate to severe SUI and has demonstrated excellent functional outcomes in systematic reviews, with complete continence rates ranging from 61.1% to 100%. However, these advantages are accompanied by high morbidity, including significant rates of explantation and erosion [4]. Stem cells have emerged as a novel treatment for many diseases. Stem cells can self-renew and differentiate into other cell types. Adult stem cells are better suited for clinical applications because they can be easily obtained without an invasive procedure, unlike embryonic stem cells (ESCs). Stem-cell therapy for SUI has been studied both preclinically and clinically. Muscle-derived progenitor cells have been used to treat SUI by promoting the regeneration of rhabdomyosphincters. Strasser *et al*. reported the first human trials to perform transurethral injection of autologous muscle-derived stem cells (MDSCs) [5]. A thickened urethral sphincter and improved sphincter contractility were noted after stem-cell transplantation. Other sources of stem cells have also been studied, such as umbilical cord blood, amniotic fluid, bone marrow, urine, and adipose tissue.

Skeletal and smooth muscles have been recognized as an essential source of progenitor or satellite cells responsible for muscle regeneration. In addition to skeletal muscle-derived cells (SkMDCs), muscle has also been identified as a valuable source of stem cells, other than satellite cells, which possess the ability to differentiate into other cell lineages called muscle-derived stem cells (MDSCs) [6].

MDSCs represent a diverse group of multipotent cells that exhibit various phenotypes based on their differentiation stage and serve as precursors to multiple connective tissue cell types, including myocytes and satellite cells. These cells can also give rise to mesenchymal, neuronal, and endothelial lineages, which play a crucial role in sphincter regeneration and the neural mechanisms associated with continence. Experimental investigations utilizing rodent, canine, and non-human primate models of stress urinary incontinence (SUI) have demonstrated their efficacy in repairing damaged urinary sphincters, showing evidence of myotube formation, neoangiogenesis, and nerve regeneration following their injection around the urethra [7]. MDSCs possess the ability to promote both structural and functional regeneration, as indicated by notable enhancements in the urethra's intravesical closure pressure and improved contractile function of the urethral sphincter. MDSCs can be harvested through a muscle biopsy performed under local anesthesia, which results in minimal morbidity. However, the isolated autologous MDSCs must be expanded in vitro and cultured for a specific duration prior to their injection into the urethral sphincter [8]. A distinct advantage of MDSCs, compared to other cell types, is that the cells injected into the urethral sphincter comprise myotubes and myofibers, which are critical for sphincter functionality and can also act as a blocking agent. Conversely, MSCs can be isolated from

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various tissues, including bone marrow, adipose tissue, umbilical cord, endometrial tissue, and oral mucosa. In addition to their regenerative properties, MSCs exhibit anti-inflammatory and immunomodulatory effects. A significant benefit of MSCs is their potential for allogenic use, enabling the selection of MSCs with superior capabilities from donors [9]. Furthermore, Adipose-Derived Stem Cells (ADSCs) are among the most frequently utilized stem cells for both autologous and allogenic transplants due to their abundance and easy accessibility from adipose tissue. ADSCs are multipotent stromal cells capable of differentiating into adipogenic, chondrogenic, myogenic, and osteogenic cells. Following periurethral injection and in the presence of specific induction factors, they can differentiate into myogenic cells, adopting a smooth muscle phenotype within approximately 8 weeks. Unlike MDSCs, ADSCs evade detection by lymphocytes and minimize immune rejection by expressing both specific and non-specific surface marker proteins. Additionally, these cells demonstrate prolonged proliferation even at low serum levels, underscoring their advantages over MDSCs [10].

Objective

This review aimed to assess the efficacy and safety of cell-based therapies for stress urinary incontinence.

Methods

Search strategy

The systematic review adhered to the PRISMA and GATHER criteria. A thorough search was undertaken to locate relevant studies on the efficacy and safety of cell-based therapies for stress urinary incontinence. The reviewers looked at four electronic databases: PubMed, Cochrane, Web of Science, and SCOPUS. Studies published from 2004 through October 2024 were included. We uploaded all of the titles and abstracts identified through electronic searches into Rayyan, removing any duplicates. All texts from papers that met the inclusion criteria based on title or abstract were collected and thoroughly inspected. Two reviewers independently evaluated the appropriateness of the extracted publications and resolved any contradictions through discussion.

Study population and selection

The PICO (Population, Intervention, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients with SUI, (ii) Intervention: cell-based therapies, (iii) Outcome: effectiveness and safety of cell-based therapies. Only primary investigations studying the administration cell-based therapies were included.

Data extraction

Two unbiased reviewers retrieved data from studies that met the inclusion criteria in a consistent and established format. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v), (vi) Type of treatment, (vii) Main outcomes (Efficacy and safety).

Quality review

We utilized the ROBINS-I technique to evaluate the risk of bias because it allows for extensive assessment of confounding, which is significant because bias owing to omitted variables is common in studies in this field. The ROBINS-I tool is intended to evaluate non-randomized investigations and can be applied to cohort designs in which participants exposed to various staffing levels are monitored over

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time. Two reviewers separately assessed the risk of bias for each paper, and disagreements were resolved through group discussion [9].
The Cochrane Risk of Bias Instrument [10] was used to conduct a critical appraisal of the identified RCTs. This tool evaluates the risk of bias in seven fields: arbitrary sequence generation, allocation secrecy, blinding of participants and employees, blinding of outcome evaluation, inadequate outcome data, selective reporting, and additional bias sources. The risk of bias in each of these domains was classified as low, unclear, or high.

Results
The results section illustrates the included 8 studies. The diverse range of countries, including Germany, Austria, Iran, Canada, and the United Kingdom, reflects a broad interest and urgent need for effective treatment options across different healthcare contexts. Notably, the studies varied in design, including clinical trials, systematic reviews, and randomized controlled trials, which enhances the robustness of the findings.

Table [1]: Shows PRISMA flowchart of the data collection process.

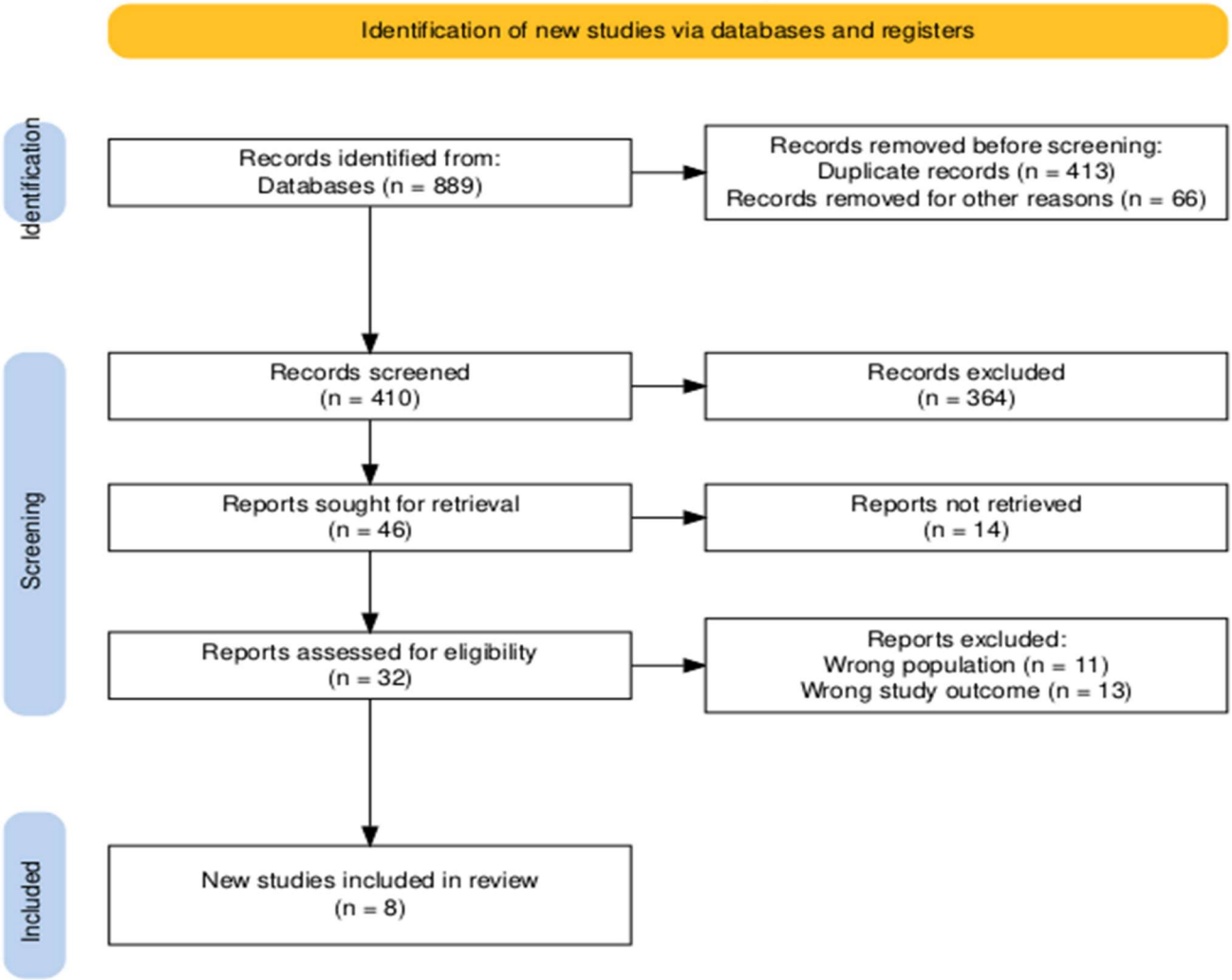

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Table [2] summarizes the major results of all the studies reviewed that have examined the use of cell therapies for stress urinary incontinence. The variation between participant numbers is also huge, from as few as 20 to as many as 143, suggesting that further research may provide much more robust measures of the safety and efficacy of cell-based therapies. Additionally, the combination of older foundational publications from 2004 and newer work from 2019 provides evidence of an expanding literature on the subject that chronicles developments and changes in treatment methodologies. Interestingly, most studies come from Austria, which would be an interesting point to investigate whether demographics, or perhaps healthcare systems, have a difference in the outcome compared to findings across other countries. Thus, in sum, this table provides a sound basis not only for subsequent discussions on the interpretative and applicative challenges of cell-based therapies in clinical practice and on how these could contribute to enhance patients' quality of life in stress urinary incontinence.

Table [2] Sociodemographic characteristics of the included participants

Author	Year of publication	Country	Study design	Participants (n)
H Strasser et.al [11]	2004	German	Clinical trial	42
Michael Mitterberger et.al [12]	2007	Austria	Clinical trial	123
Michael Mitterberger et.al [13]	2008	University of Innsbruck, Austria.	Clinical trial	20
M Aref-Adib et.al [14]	2013	NM	Systematic review	Eight studies
Hannes Strasser et.al [15]	2007	Austria	a randomised controlled trial	63
H Strasser et.al [16]	2007	Austria	a randomised controlled trial	63
Sharifiaghdas et al. [17]	2019	iran	Prospective interventional case series	20
Jankowski et al. [18]	2018	Canada, United Kingdom, Germany	Interventional randomized placebo-controlled trial	143

Table [3] shows various studies on the safety and efficacy of using cell-based therapy to treat stress urinary incontinence (SUI), adding a burden to a women's everyday life. This is promising for results across several studies, and particularly for the success of autologous stem cells, such as fibroblasts and myoblasts. Here, for instance, of the 35 patients in a study of fibroblast therapy, 35 went on to have complete resolution of incontinence symptoms without postoperative complications. The treatment was shown to succeed in another significant study with 123 women, with 79% being completely continent one year post treatment. In addition, a randomized controlled trial demonstrated that 90.5% of patients injected with autologous myoblasts and fibroblasts achieved complete continence versus negligible

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9.5% in patients in the collagen injection group, showing the superiority of cell based therapies over the existing treatments. It is of interest that while some studies have shown relatively high placebo response rates with autologous muscle derived cells, interim analysis appeared to support a potential for beneficial effects if performed in more rigorous conditions. Overall, with regards to incontinence scores, urethral thickness, and sphincter contractility, most studies show a significant increase in following intervention, however challenges persist for data quality & maturity consolidation. Finally, SUI cell based therapies are clearly safe and effective alternatives, yet methodologies and limitations, including the need for more sophisticated multi center randomization and longer follow up, warrant additional research. Further investigation of these promising findings could refine treatment protocols, thereby improving both the quality of life and health of many individuals with SUI.

Table [3] Clinical characteristics and outcomes of the included studies

Study name	Cell type	Key findings	Conclusion
Stem cell therapy for urinary incontinence	fibroblasts	In 35 patients urinary incontinence could be completely cured. In seven patients who had undergone multiple surgical procedures and radiotherapy urinary incontinence improved. No side effects or complications were encountered postoperatively.	The experimental as well as the clinical data clearly demonstrate that urinary incontinence can be treated effectively with autologous stem cells.
Autologous myoblasts and fibroblasts for female stress incontinence: a 1-year follow-up in 123 patients	autologous myoblasts and fibroblasts	At 1 year after implanting the cells, 94 of the 119 women (79%) were completely continent, 16 (13%) had a substantial improvement and nine (8%) a slight improvement. Four patients were lost to follow-up. The incontinence and I-QOL scores, and the thickness, contractility and electromyographic activity of the rhabdosphincter were significantly improved after treatment.	These results show the efficacy and safety of transferring autologous myoblasts and fibroblasts in the treatment of female SUI, after a follow-up of 1 year.
Adult stem cell therapy of female stress urinary incontinence	autologous fibroblasts and myoblasts	Eighteen of 20 patients were cured 1 yr. after injection of autologous stem cells and in 2 patients SUI was improved. Two years after therapy 16 of the 18 patients presented as cured, 2 others were improved, and 2 were lost to follow-up. Incontinence and quality-of-life scores were significantly improved postoperatively. The thickness of urethra and rhabdosphincter as well as activity and contractility of the rhabdosphincter were also statistically significantly increased after therapy.	Clinical results demonstrate that SUI can be treated effectively with autologous stem cells. The present data support the conclusion that this therapeutic concept represents an elegant and minimally invasive treatment modality to treat SUI.

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Stem cell therapy for stress urinary incontinence: a systematic review in human subjects	NM	Incontinence score: 4 studies describe significant improvement. Quality of life: significant improvement in 4 studies. Urodynamic outcomes: 4 studies show significant improvement in contractility of urethral sphincter; 3 studies demonstrate no change in bladder capacity and significant reduction in residual volume; significant improvement in urinary flow 3 studies, although 2 found no difference; increase in leak point pressure and detrusor pressure in 3 studies. Urethral ultrasound: 3 studies found significant increases in rhabdosphincter thickness and contractility. Urethral EMG: 2 studies found significant increases in the EMG at rest and at contraction.	Data suggest that SC treatment for SUI is safe and effective in the short term. However, the quality and maturity of the data are limited.
Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial	Autologous myoblasts and fibroblasts vs collagen	At the 12-month follow-up, 38 of 42 women (90.5%) injected with autologous cells achieved complete continence, compared to only 2 of 21 (9.5%) treated with collagen. The median incontinence score improved from 6.0 to 0 for autologous cell patients, while it remained at 6.0 (IQR 3.5-6.0) for collagen patients ($p<0.0001$). Additionally, the mean thickness of the rhabdosphincter increased from 2.13 mm to 3.38 mm in the autologous cell group versus 2.32 mm in the collagen group ($p<0.0001$), and contractility rose from 0.58 mm to 1.56 mm for autologous cells and 0.67 mm for collagen ($p<0.0001$). No adverse effects were reported among the 63 patients.	ultrasonography-guided injections of autologous myoblasts and fibroblasts demonstrate significant superiority over conventional collagen injections in treating urinary stress incontinence, as evidenced by marked improvements in incontinence scores, rhabdosphincter thickness, and contractility. These findings suggest that autologous cell therapy is not only effective but also safe, making it a promising alternative for patients with this condition.
Transurethral ultrasonography-guided injection of adult	myoblasts and fibroblasts vs collagen	After a follow-up of 12 months incontinence was cured in 39 women and 11 men after injection of autologous myoblasts and fibroblasts.	The present clinical results demonstrate that, in contrast to injections of collagen, urinary

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autologous stem cells versus transurethral endoscopic injection of collagen in treatment of urinary incontinence		Mean quality of life score (51.38 preoperatively, 104.06 postoperatively), thickness of urethra and rhabdosphincter (2.103 mm preoperatively, 3.303 mm postoperatively) as well as contractility of the rhabdosphincter (0.56 mm preoperatively, 1.462 mm postoperatively) were improved postoperatively. Only in two patients treated with injections of collagen incontinence was cured.	incontinence can be treated effectively with ultrasonography-guided injections of autologous myo- and fibroblasts.
Autologous muscle-derived cell injection for treatment of female stress urinary incontinence: a single-arm clinical trial with 24-months follow-up.	MDSCs	A total of 20 eligible female patients with the chief complaint of SUI that was unresponsive to conserva-tive management, was enrolled in the trial, 17 of whom completed all follow-up visits. At 12th months, 10 (59%) patients had complete response, whereas 2 (12%) and 5 (29%) patients had partial and no response, respectively. At 24th months, relapse of SUI in 5 out of 10 complete responders (29%) and 2 out of 2 partial responders to the treatment, respectively. The intervention produced no serious AE during the trial.	MDC therapy was a minimally invasive and safe procedure for treatment of female patients with pure SUI. However, currently, the efficacy of this type of treatment for SUI is not sufficiently high and multi-center randomized clinical trials are required to be conducted before reaching a concrete conclusion.
A double-blind, randomized, placebo-controlled clinical trial evaluating the safety and efficacy of autologous muscle derived cells in female subjects with stress urinary incontinence	autologous muscle derived cells AMDC	autologous muscle derived cells for urinary sphincter repair (AMDC-USR) was safe and well-tolerated with no product-related serious adverse events or discontinuations due to adverse events. Interim analysis revealed an unexpectedly high placebo response rate (90%) using the composite primary outcome which prevented assessment of treatment effect as designed and thus enrollment was halted at 61% of planned subjects. Post hoc analyses suggested that more stringent endpoints lowered placebo response rates and revealed a possible treatment effect.	the study demonstrated that (AMDC-USR) are safe and well-tolerated in female subjects with stress urinary incontinence. Despite the unexpectedly high placebo response rate, which complicated the assessment of efficacy, post hoc analyses indicate potential treatment benefits when using more stringent endpoints.

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Table [4] shows risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
H Strasser et.al [11]	Low	Some Concerns	Low	Low	Low	Low	Low	Low
Hannes Strasser et.al [15]	Low	Low	Low	Low	Low	Some Concerns	Low	Low
Michael Mitterberger et.al [13]	Some Concerns	Some Concerns	Low	Low	Low	Low	Low	Low
Jankowski et al. [18]	Low	Low	Low	Low	Low	Some Concerns	Low	Low
Michael Mitterberger et.al [12]	Some Concerns	Some Concerns	Low	Low	Low	Some Concerns	Low	Moderate
H Strasser et.al [16]	Low	Mod	Mod	Mod	Low	Mod	Low	Moderate
Sharifiaghdas et al. [17]	Some Concerns	Low	Some Concerns	Some Concerns	Low	Low	Low	Moderate
M Aref-Adib et.al [14]	Some Concerns	Some Concerns	Low	Low	Low	Some Concerns	Some Concerns	Moderate

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Discussion

The recent studies on the effectiveness of autologous cell therapy for urinary incontinence highlight a promising advancement in treatment, particularly for patients with stress urinary incontinence (SUI) that remains unresponsive to conservative management. Strasser et al. [11] demonstrated a complete cure in 35 patients without any postoperative complications, suggesting a strong safety profile for this intervention. This is echoed in findings by Mitterberger et al. [12] and [13], where substantial improvements in incontinence were observed in a significant majority of women following autologous stem cell injections, with 79% achieving complete continence 12 months post-treatment. These results underscore the potential of cultivating a patient's own cells for therapeutic use, facilitating both improvement in urinary function and enhancing quality of life. Further corroboration of these findings comes from Aref-Adib et al. [14], who summarized various studies indicating significant improvements in both incontinence and quality of life scores, alongside favorable urodynamic outcomes, thereby reinforcing the positive impact of such interventions on rhabdosphincter contractility and bladder function. Strasser et al. [15] added depth to this inquiry, revealing marked differences in outcomes between patients treated with autologous cells versus collagen, where the latter group showed negligible improvement. This stark contrast emphasizes the superiority of autologous cell therapy over traditional approaches. Moreover, Strasser et al. [16] reinforced these conclusions by reporting significant enhancements in both urethral thickness and contractility following myoblast and fibroblast injections, with remarkably few adverse effects. While the study by Sharifiaghdas et al. [17] reported a relapse rate in 29% of complete responders after two years, the absence of serious adverse events throughout the trial suggests that these therapies maintain a favorable safety profile over time. Finally, Jankowski et al. [18] highlighted the safety and tolerability of autologous muscle-derived cell treatments, though concerns around high placebo response rates necessitate careful interpretation of these findings. Together, these studies strongly advocate for the clinical promise of autologous cell therapy in treating SUI, illustrating not only its efficacy but also its minimal risks of adverse effects, thus setting a new standard for future approaches in managing this common but often debilitating condition.

Conclusion

The collective findings from the previously mentioned studies underscore the efficacy and safety of using autologous cells for the treatment of urinary incontinence, particularly for stress urinary incontinence (SUI). A significant number of patients experienced complete or substantial improvements in incontinence, along with notable enhancements in quality of life and measurable physiological improvements in rhabdosphincter thickness, contractility, and electromyographic activity. The results highlight that procedures involving autologous stem cells or myoblast injections yield superior outcomes compared to traditional treatments like collagen injection, with minimal to no reported complications. These studies support the promise of autologous cell therapy as a viable option for patients with refractory SUI, while also indicating the need for further research to optimize protocols and minimize variability in responses.

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Conflict of interests

The authors declare no conflict of interest.

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