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THE SYSTEMATIC REVIEW OF STEM CELL THERAPY FOR STRESS URINARY INCONTINENCE

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ABSTRACT

Background: *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.*

The aim: *This study aims to show stem cell therapy for stress urinary incontinence.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database the results of our search brought up 133 articles, whereas the results of our search on SagePub brought up 54 articles. The results of the search conducted for the last year of 2013 yielded a total 89 articles for PubMed and 41 articles for SagePub. The result from title screening, a total 9 articles for PubMed and 15 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Comprehensive comparisons between stem cell-based approaches and existing therapies are a prerequisite to rendering stem cell treatment as the predominant strategy for treating intractable urological disorders in the future.*

Keyword: *Stem cell, stress urinary incontinence.*

INTRODUCTION

The incidence of urinary incontinence (UI) is approximately 10%–40% in women, affecting one to two hundred million women worldwide. 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. SUI can arise from anatomic incontinence, also known as hypermobile urethra and intrinsic sphincter deficiency (ISD). Surgical treatments for anatomical incontinence include bladder neck suspension and insertion of a midurethral sling. Surgical treatment for ISD involves sling implantation and urethral submucosal injection of blocking agents (fat tissue, Teflon, collagen, or silicone). Nevertheless, an optimal treatment for all types of incontinence has not been established.[1,2]

Continence and micturition are achieved by a complex interplay of anatomical structures such as the urethral sphincter, detrusor, bladder neck, urethral smooth muscle, nerves, vascular plexus and the surrounding tissue support. There is an active and passive component contributing to intraurethral pressure. This pressure is mainly generated by the rhabdosphincter (external urethral sphincter, striated muscles, intentional) and the lissosphincter (internal urethral sphincter or “Hessian loop”, smooth muscles, unintentional)–both belonging to the active component. Normally, the urethral pressure exceeds bladder pressure, resulting in continence. The proximal urethra and bladder are both within the pelvis and an increased intra-abdominal pressure is transmitted to both urethra and bladder equally. In case of an intact pelvic floor, this leaves the pressure differential unchanged and therefore results in urine remaining within the bladder (passive component). Normal voiding is initiated by the parasympathetic nervous system through the pelvic nerve. As a result, urethral pressure falls (relaxation of sphincter) and bladder pressure rises (detrusor contraction). During the filling phase, sympathetic nervous activity inhibits the detrusor and activates the smooth urethral muscles (unintentional), increasing the outlet resistance through hypogastric nerves and stimulation of alpha-adrenoreceptors.[3,4]

Stem cells can differentiate into a range of cell types, with a characteristic capacity for continuous self-renewal. These cells are thereby self-sustaining and can differentiate into progenitor cells to replace aging cells undergoing apoptosis. This potential has rendered stem cell research a predominant area of interest in the field of regenerative medicine, which focuses on fundamental over conservative treatments.[5,6]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast stem cell therapy for stress urinary incontinence. It is possible to accomplish this by researching or investigating stem cell therapy for stress urinary incontinence. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about stem cell therapy for stress urinary incontinence. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " stem cell therapy for stress urinary incontinence.” as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Stem cell"*[MeSH Subheading] OR* "Stem cell therapy"*[All Fields] OR* "Urinary incontinence*” [All Fields]) AND (*"Stress urinary incontinence"*[All Fields] OR "* effects of stem cell therapy *"[All Fields]) AND (*"Mechanism of stress urinary incontinence"*[All Fields]) OR (*"Stem cell and stress urinary incontinence” *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

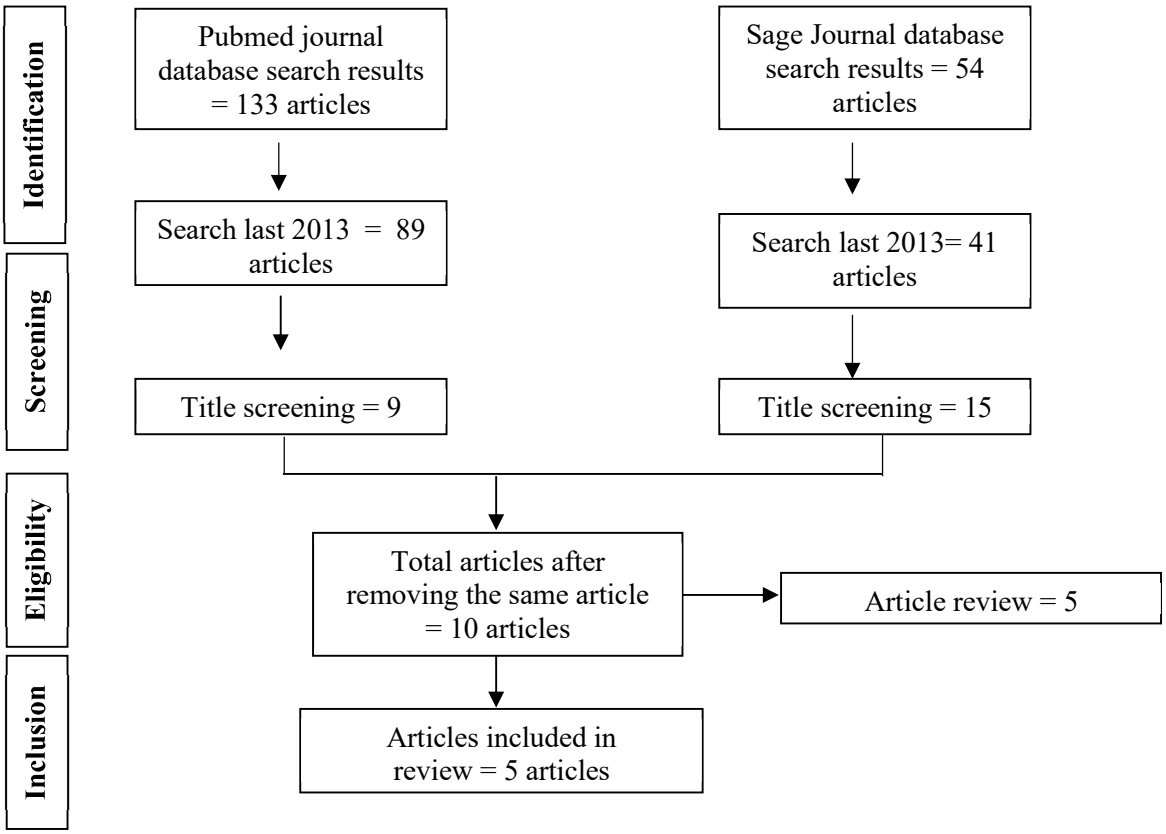

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 133 articles, whereas the results of our search on SagePub brought up 54 articles. The results of the search conducted for the last year of 2013 yielded a total 89 articles for PubMed and 41 articles for SagePub. The result from title screening, a total 9 articles for PubMed and 15 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Arraz, MG *et al* (2020)[7] showed intraurethral application of stem cells derived from adipose tissue is a safe and feasible procedure to treat urinary incontinence after radical prostatectomy or in female stress urinary incontinence. A statistically significant difference was obtained for pad-test improvement in 3/8 men and 5/10 women. Our results encourage studies to confirm safety and to analyze efficacy.

Barakat, B *et al* (2020)[8] showed Despite many challenges in stem cell-based therapy for treating SUI, it appears to provide, in both male and female patients, acceptable functional results with minimal side-effects and complications. In the future, more clinical trials should be funded in order to optimise stem cell-based therapy and evaluate long-term outcomes.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Arranz, MG *et al*., 2020[7]	Spain	Prospective, nonrandomized phase I-IIa clinical trials	19 participants	After 4 to 6 weeks and under sedation, endoscopic intraurethral injection of the cells was performed. On each visit (baseline, 1, 3, 6, and 12 months), clinical parameters were measured, and blood samples, urine culture, and uroflowmetry were performed. Every patient underwent an urethrocystoscopy and urodynamic studies on the first and last visit. Data from pad test, quality-of-life and incontinence questionnaires, and pads used per day were collected at every visit. Statistical analysis was done by Wilcoxon signed-rank test. No adverse effects were observed. Three men (37.5%) and five women (50%) showed an objective improvement of >50% ($P < .05$) and a subjective improvement of 70% to 80% from baseline.
Barakat, B *et al*., 2020[8]	Germany	Cohort study	15 trials	We identified four clinical trials using local injections of adipose-derived stem cells (ADSCs), 11 trails with muscle-derived stem cells (MDSCs), and two trails with human umbilical cord blood stem cells (HUCBs) and total nucleated cells (TNCs). The median improvement rate of intrinsic sphincter deficiency after ADSCs, MDSCs, TNCs, HUCBs injections were 88%, 77%, 89%, 36% (improvement rate: 1–2 pads) at a mean (range) follow-up of 6 (1–72) months. The cell sources, methods of cell processing, cell number, and implantation techniques differed considerably between studies. Most of the periurethral injections were at the 3, 5, 7, and 9 o'clock positions and for submucosa were at the 4, 6, and 8 o'clock positions. No significant postoperative complications were reported.
Williams, JK *et al*., 2016[9]	USA	Cohort study		Cell therapy is currently proposed to restore functional muscle cells and aid in closure of the sphincter in women with sphincter-associated incontinence. The clinical trials have included small

				numbers of patients and results vary depending on the patient cohorts, and the cells used. Results of preclinical studies also vary, but report a more favorable outcome. This difference is most likely explained by animal modeling not being directly translatable to the human condition. However, preclinical studies have identified an exciting new approach to regeneration of the urinary sphincter by using the components of cells (secretomes) or chemokines that home reparative cells to the sites of injury.
Abufaraj, M *et al*., 2021[10]	USA	Prospective study		In the 2017e2018 cycle, stress urinary incontinence was the most prevalent subtype (45.9%; 95% confidence interval, 42.1e49.7), followed by urgency urinary incontinence (31.1%; 95% confidence interval, 28.6e33.6) and mixed urinary incontinence (18.1%; 95% confidence interval, 15.7e20.5). The prevalence rates of urgency and mixed urinary incontinence were higher in women aged 60 years and older (urgency, 49.5% [95% confidence interval, 43.9e55.2]; mixed, 31.4% [95% confidence interval, 26.2e36.6]) than in those aged 40 to 59 years (urgency, 27.9% [95% confidence interval, 23.6e32.1]; mixed, 15.9% [95% confidence interval, 12.9e19.0]) and those aged 20 to 39 years (urgency, 17.6% [95% confidence interval, 13.8e21.5]; mixed, 8.3% [95% confidence interval, 5.4e11.3]). The overall prevalence of stress and mixed urinary incontinence was stable throughout 2005 to 2018 (both Ptrend¼.3), with increases in mixed urinary incontinence among women aged 60 years and older (P¼.001). The prevalence of urgency urinary incontinence significantly increased, particularly among women aged 60 years and older (both P¼.002). Age, obesity, smoking, comorbidities, and postmenopausal hormone therapy were associated with

				higher prevalence of all types of urinary incontinence. Black women were less likely to report stress urinary incontinence but more likely to report urgency urinary incontinence.
Zhou, HH *et al*., 2018[11]	China	Case–control and cohort studies	74,883 adult females	Thirteen studies (8 cohorts and 5 case–controls) were included in our meta-analysis, with a total of 74,883 adult females. Our meta-analysis showed that compared with nulliparity, ORs of women with 1, 2, and ≥3 parity were 1.43 [95% confidence interval (95% CI): 0.90–2.28; I^2=81.4%; n=4], 1.50 (95% CI: 1.02–2.20; I^2=82.5%; n=4), and 1.58 (95% CI: 1.22–2.03; I^2=70.1%; n=7) compared with nulliparity. The OR for any multiparity to nulliparity was 1.68 (95% CI: 1.39–2.03; I^2=0%; n=4). Subgroup analysis showed that parity was associated with an increased risk of stress UI (OR=2.32, 95% CI: 1.41–3.81; I^2=0%; n=2; 1 compared with null parity) but not urgent UI; However, the definition of parity varies across studies and studies defined parity as delivery times showed higher pooled OR than those not. Sensitivity analysis showed our results were stable.

Williams, JK *et al* (2016)[9] showed Preclinical research in animal models of ISD/SUI and studies in humans have shown the feasibility of cellular therapy as a treatment alternative. However, in view of the promising, but rather preliminary clinical results, it seems reasonable that before starting new randomized controlled trials based on existing information, novel approaches should be evaluated in optimized preclinical models, using well defined cells or secretomes. Such endeavors may aid in the development of clinically applicable cellular therapy with satisfactory long-term outcome.

Abufaraj, M *et al* (2021)[10] showed Although the estimated overall prevalence of stress and mixed urinary incontinence remained stable from 2005 to 2018, the prevalence of urgency and mixed urinary incontinence significantly increased among women aged 60 years and older. All subtypes of urinary incontinence were higher among women with obesity and comorbidities, those who used postmenopausal hormone therapy, and those who smoke.

Zhou, HH *et al* (2018)[11] showed UI is a disease associated with multiple mechanisms. Bladder overactivity, poor bladder control, and pelvic floor musculature impairment were all the direct causes of UI. The results are attributed to pelvic floor musculature and connective tissue injury during the process of parturition that influences the normal urinary continence function. However, this was also highly dependent on the type of delivery. In some studies, caesarean delivery was not associated with risk of UI. In our meta-analysis, most of the studies did not report about the delivery type. As a result, the identification of the effects of delivery type becomes challenging.

DISCUSSION

Stress urinary incontinence (SUI) is caused by a variety of factors and typically be attributed to mechanical and functional factors. Myogenic, connective tissue, and hormonal alterations are significant variables. In addition, muscle cell density falls because of natural aging process and decreased muscle function in rhabdosphincter, with the overall volume reducing from 88% at birth to 34% in the 90th year of life. Female SUI is frequently caused by multiple factors, including dysfunctions of the sphincter and nerve injury. The mid-urethral sling has the benefit of requiring less intervention time. The rate of any reoperation was 5.5–6.9% in long term follow-up. However, several organizations has frequently issued

warnings against the use of mesh materials in the treatment of female urinary incontinence as the result of many severe adverse events.[12,13]

Stem cells are classically thought to improve tissue repair via multilineage differentiation and self-renewal. Stem cells may also exert a therapeutic effect via the secretion of bioactive factors that have antiapoptotic,mantiscarring, neovascularization, and immunomodulatory effects on innate tissues and can direct innate stem and progenitor cells to the area of injury. Multiple treatment avenues using stem cells for voiding dysfunction, especially SUI, have been evaluated with preclinical animal models and clinical trials demonstrating their potential to restore function via direct effects on the underlying mechanisms that lead to incontinence or voiding dysfunction.[14,15]

Stem cells are classically defined by their self-renewal based long-term survival and their flexible fate, being able to differentiate into other cell types. However, as simple as the concept seems to be, the accurate identification, isolation and transplantation of stem cells could be more intricate than originally thought. For example, the functional distinction between stem cells and their progenitor cells remains ambiguous. This should be taken in consideration when planning stem cell therapies; a successful therapy may require other progenitor cells to turn on differentiation and proliferation signals of the parent stem cell. As well, the transition of the stem cell between quiescent and active stages is a dynamic process that challenges the accurate prediction of stem cell behaviour in different environments.[16]

CONCLUSION

Comprehensive comparisons between stem cell-based approaches and existing therapies are a prerequisite to rendering stem cell treatment as the predominant strategy for treating intractable urological disorders in the future.

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