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SYSTEMATIC REVIEW

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Evaluation of the efficacy of stem cell therapy in erectile dysfunction after radical prostatectomy: a comprehensive systematic review

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Abstract

Around 68% patients undergoing radical prostatectomy face postoperative erectile dysfunction. This systematic review aims to investigate the studies pertaining to efficacy of stem cell therapy in alleviating erectile dysfunction (ED) of radical prostatectomy (RP) patients. Furthermore, it provides evidence-based potential benefits of stem cell therapy in addressing erectile dysfunction of those patients. A systematic literature search from PubMed, Google Scholar, Science Direct and clinicaltrial.gov databases was conducted for the clinical trials evaluating efficacy and safety of stem cell therapy in post-prostatectomy erectile dysfunction. The inclusion criteria pertained to the studies reporting pre- and post-outcome erectile function and safety results. Cochrane Robins I was employed for the quality and bias risk. Four studies were finally included. The studies were of high quality as revealed from the quality assessment results. They were the non-randomized human-based clinical trials. Patients follow-up ranged from 3 to 12 months. Intercourse satisfaction scores were improved after 6 and 12 months of stem cell therapy. No serious adversities were reported during and after the study period. It was thus a safe therapeutic option as per these results. This study evaluated the role of stem cell therapy in post-RP ED. The included studies depicted its efficacy and safety. The information on stem cell therapy for ED was limited, however it could provide foundation for future research. Large-scale human studies with robust research designs would bring more objectivity and conclusive evidence.

Keywords

Post-prostatectomy; Erectile dysfunction; Stem-cell therapy

1. Introduction

Prostate cancer is among the most diagnosed cancers. Prostatectomy compared to the conservative treatment strategies is the only therapy associated with improved survival in localized prostate carcinoma patients. It is the most frequently employed first-line treatment. The erectile dysfunction (ED) following radical prostatectomy (RP) is a concern for the patients and clinicians, despite the advances in understanding the prostate surgical anatomy and development of minimally invasive surgical procedures [1]. ED is a multifaceted and prevalent male sexual dysfunction involving change in the biological, relational, or psychological components of erectile response. ED periodically affects significant percentage of men who cannot obtain or sustain sufficient/required erection [2]. Men and their partner's life quality are negatively impacted by ED, which is an issue even after the cancer treatment concerns have lapsed [3].

The incidence rate of ED after prostatectomy varies between 6% and 68%. More young men have been diagnosed with prostate cancer in the past few decades which has triggered the significance of erectile function recovery after prostate cancer treatment. Preserving the patients' life quality has thus been focused [1]. Postoperative ED is more prevalent in patients with localized prostate cancer undergoing pelvic surgery such as RP because of the neuropraxia. The surgical intervention itself is an important aspect of post-RP ED since the surgical skills and expertise are imperative in the development of post-RP ED. Local inflammation and ischemia are developed after the local trauma of cutting, coagulation, traction, or compression of pelvic structures to improve the visualization of operating area. The cavernous nerves are affected to cause diminished local oxygenation, and pro-apoptotic and pro-fibrotic alterations in corpora cavernosum [4]. ED is prevalent with RP surgery despite the introduction of nerve-sparing RP thirty years back.

The nerve-sparing RP results in minor changes that are not

readily apparent to the surgeons, although it spares the cavernosal nerves. Cavernosal nerves undergo Wallerian degeneration because of these changes and subsequently dissociate from the corpora cavernosa [5]. ED after prostatectomy is a frequent complication even in this era of medicine and surgery. It is aimed herein to review the existing evidence from literature regarding the role and efficacy of stem cell therapy (SCT) in treating post-RP ED, and make evidence-based assessment of the potential benefits of SCT in addressing ED in these cohorts of patients.

The need for ED treatment has been realised since long and several studies have been conducted. Pharmacotherapy, including phosphodiesterase type 5 inhibitors, is the main treatment for post-prostatectomy ED males [6]. SCT, gene transplantation, growth factors, low-intensity extracorporeal shockwave therapy, immunophilins, and other pharmacological approaches have also improved the erectile function in experimental models with cavernous nerve damage. Many of the above methods can enhance erectile function after RP, if developed as clinically useful, safe and effective interventions [7]. The approaches including low-intensity extracorporeal shock wave therapy and SCT are explored as effective treatments of post-RP ED. Stem cells are investigated regarding their role in curing ED following RP. SCT is applied to various clinical diseases owing to its immunoregulatory, immunosuppressive, and regenerative effects [5].

SCT has been proposed as ED treatment because it can repair the structural damage of penile tissue by differentiating into endothelial, neuronal or smooth muscle cells. These cell lines show *in vitro* stem cell differentiation, and the preclinical research has demonstrated improved ED after the SCT in animal models. Adipose tissue-, bone marrow-, muscle- and embryonic-derived stem cells are the primary types employed in ED preclinical investigations. The documented clinical trials utilizing stem cells have yielded positive outcomes [8]. Many clinical trials of stem cell treatment are in progress, and reveal that SCT is safe and assists in better erectile function for individuals with post-RP ED [9]. A systematic review also concludes that the evidence from literature may act as the foundation for using therapeutic potential of SCT in ED treatment [10]. Herein, the current evidence from literature is assessed in this regard.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to report this systematic review. The PROSPERO registration number of this review is “CRD42023432814”.

2.1 Search strategy and study selection

From inception to April 2023, two investigators independently searched PubMed, Google Scholar, Science Direct and clinicaltrial.gov databases for studies evaluating SCT efficacy in improving ED of post-RP patients. The electronic search used keywords as “prostatectomy”, “erectile dysfunction”, “bone marrow”, “adipose cell”, “cell therapy” and “stem cell”. The references of screened full-text studies were also checked for potentially eligible trials. Inclusion criteria were followed to determine the eligible studies. Criteria required the study population to consist of post-RP-ED. SCT was employed as the intervention. Studies not evaluating the pre- and post-study outcomes or only the observational studies with no follow-up, case series, case reports or animal studies were excluded. The most comprehensive study was utilised if several studies had the same population. Any discrepancy was resolved through discussion and adjudication by a senior reviewer. The included studies were peer-reviewed and published.

2.2 Screening and data extraction

Articles of improper titles were excluded in the initial step of selection. Abstracts and full texts fulfilling the inclusion criteria were assessed in the second phase. Endnote X8 (Clarivate^{TM}, Philadelphia, PA, USA) was employed to organize and evaluate the titles and abstracts for duplicate entries. A double screening ensured the high-quality findings where one assessment was made for titles and abstracts, and other for entire texts. A piloted data-extraction sheet gathered the information of study period, study design, sample size, study region and age distribution. The predetermined endpoints of trial were Erectile Function (EF) and adverse events. Two investigators independently performed the data extraction, and discrepancies were consensually resolved without simplifications or assumptions. Primary outcomes of this study were the adverse events and EF improvement.

2.3 Quality assessment of individual studies

Cochrane Robins I assessed the methodological quality and bias risk of non-randomized human trials included in this review [11]. This tool analysed the confounding participant selection, intervention categorization, deviation from interventions, missing data, outcome measurement, and selection of reported findings. Evaluations depicted that the response for each criterion was classified as low, high or unclear bias risk.

2.4 Stem cell preparation

Stem cells have been utilized in literature including those of bone marrow, adipose tissue, umbilical cords and placentas. These cells are prepared through two approaches. The first is to extract stem cells from donor tissue and use as such or cultivate to increase number. The second approach is specific to adipose-derived stem cells (ADSC) and uses Stromal Vascular Fraction (SVF). This is derived from adipose tissue of a donor and involves the centrifugation of extracted fat tissue. SVF is the by-product of this centrifugation. It contains stem cells and precursor endothelial cells, growth factors and cells modulating the immune system. The stem cells in a culture yield higher quantity than those found in SVF. The additional components in SVF may increase collaboration with the stem cells to improve clinical outcomes. The definitive conclusion on this comparison is yet to be established [8].

3. Results

3.1 Search results

The search identified 156 studies to screen for relevance. The full text of relevant abstracts was analysed where 42 articles were evaluated and only four matched the inclusion criteria and thus selected for the review. Fig. 1 shows the PRISMA flow diagram of study selection depicting the search and selection process.

3.2 Quality assessment results

Cochrane Robins I exhibited low bias risk for all four included studies. Because of the low bias risk, they are considered high-quality studies as per the quality assessment. Only one study by Yiou *et al.* [12] depicted moderate bias risk regarding the selected participants. No included study showed unsatisfactory results as presented in Table 1.

3.3 Characteristics and outcome of included study

Table 1 presents the main characteristics of four included studies [12–15]. They were published between 2015 and 2018 with sample size from 6 to 21 for a total of 65. Follow-up of the patients continued from 3 to 12 months. All four studies were non-randomized human clinical trials.

3.4 Stem cells type and preparation

Haahr *et al.* [15] used adipose-derived regenerative cells (ADRC) from abdominal adipose tissue collected under general anesthesia. The fresh ADRC were isolated from lipoaspirate and injected into corpus cavernosum within two hours of harvesting. Cell processing was performed on an automated processing Celution® 800/CRS system (Cytori Therapeutics, San Diego, CA, USA) [14, 15]. Yiou *et al.* [12] phase I study employed autologous bone marrow mononuclear stem cells (BM-MNC) with a dose of 10^9 cells. One intracavernous injection of BM-MNC administering 10^9 cells in 6 months with higher doses of stem cells (2×10^7, 2×10^8, 1×10^9 or 2×10^9 stem cells). Phase II study of 2017 reported the optimal dose as 1×10^9 [13].

3.5 Outcome measures

The included studies reported no severe adverse events after the SCT in post-RP ED patients. Haahr *et al.* [15] 2016 had a small sample of 17 participants. The baseline intercourse satisfaction (IS) was 7 ± 3.25 and increased to 17 ± 8.13 after the treatment. However, the follow-up duration was only six months. Haahr *et al.* [14] 2018 study had 21 participants. The baseline IS was recorded as 6 ± 2.22 and increased to 8 ± 5.93 following the treatment. The follow-up period was 12 months which assessed the long-term effects of treatment. Yiou *et al.* [12] 2015 study had 12 participants. The data included baseline IS and EF measurements. IS at baseline was 3.9 ± 2.5 and improved to 6.8 ± 3.6 after the treatment. EF at baseline was 7.3 ± 4.5 and improved to 17.4 ± 8.9 after treatment. The follow-up period was six months indicating notable improvements in IS and EF within this time frame. Yiou *et al.* [13] 2017 included 9 participants. The baseline measurements for IS and EF were recorded as 2.2 ± 3.4 and 3.7 ± 4.1, respectively. Substantial improvements in IS with a mean of 7.8 ± 3.1, and EF of 18 ± 8.3 were measured after the treatment. The follow-up period was 12 months for assessing the treatment's sustained impact on IS and EF [12, 13]. Two included studies explained the changes in International Index of Erectile Function-5 (IIEF-15) scores after BM-MNC injections at 6 and 12 months compared to baseline, including scores of EF, orgasmic function, overall satisfaction, and IS (Table 2). No serious adversities were reported except the minor and reversible side effects. All events were resolved without intervention (Table 3).

4. Discussion

In this study, the literature was systematically and comprehensively reviewed to evaluate the efficacy of stem cell therapy (SCT) in post-RP ED. The findings demonstrated that IS scores were improved after the SCT at 6 and 12 months follow-up time. No serious adverse events were reported during and after the study period which made it a safe therapeutic option as per these results. The scarcity of studies on this topic was identified during the elaborated literature search which resulted in the inclusion of only four studies.

Similar to these results, Xu and Wang stated that after RP, penile rehabilitation using SCT, nerve transplantation, low-intensity extracorporeal shockwave therapy, and erythropoietin were highly effective. Authors further explained that the focus of ED treatment was symptom remission. SCT might treat the condition's underlying cause by altering pathophysiological modifications producing ED. SCT had undergone several clinical trials to reveal that it could safely enhance EF in people with post-RP ED [9]. Hansen *et al.* [16] described improvement in EF by utilizing SCT as a safe option. This claim of stem cells as a viable treatment for ED needed further evidence from large randomized human phase 2 studies. However, the outcomes of animal and human trials for the stem cells as restorative therapy are encouraging [16].

Yiou R narrated that RP remained the standard treatment for organ-confined prostate cancer. RP carried a substantial risk of ED because of the damage to penile neurovascular bundles that run along the posterolateral portions of prostate, despite the ongoing technological advancements. ED following RP had the neurogenic and vasculogenic factors since these bundles were comprised of cavernous arteries and nerves. The functional outcome of RP was determined by the degree to which penile neurovascular bundles and intrapelvic auxiliary pudendal arteries were spared. The chain of events resulting in penile fibrosis could be stopped through the early treatment with either oral erectogenic medications or intracavernous injections of vasoactive substances. Intracavernous stem cell injection was the main component of new therapy for post-RP ED developed in response to pathophysiology insights provided *via* animal studies. These injections had been studied in the preclinical trials as a potential treatment for complicated range of cell damage by RP, and to enhance EF. Adipose tissue and bone marrow were the potential sources of stem cells [17].

Pérez *et al.* [18] described that the action mechanism of mesenchymal stem cells was uncertain. Stem cells were believed

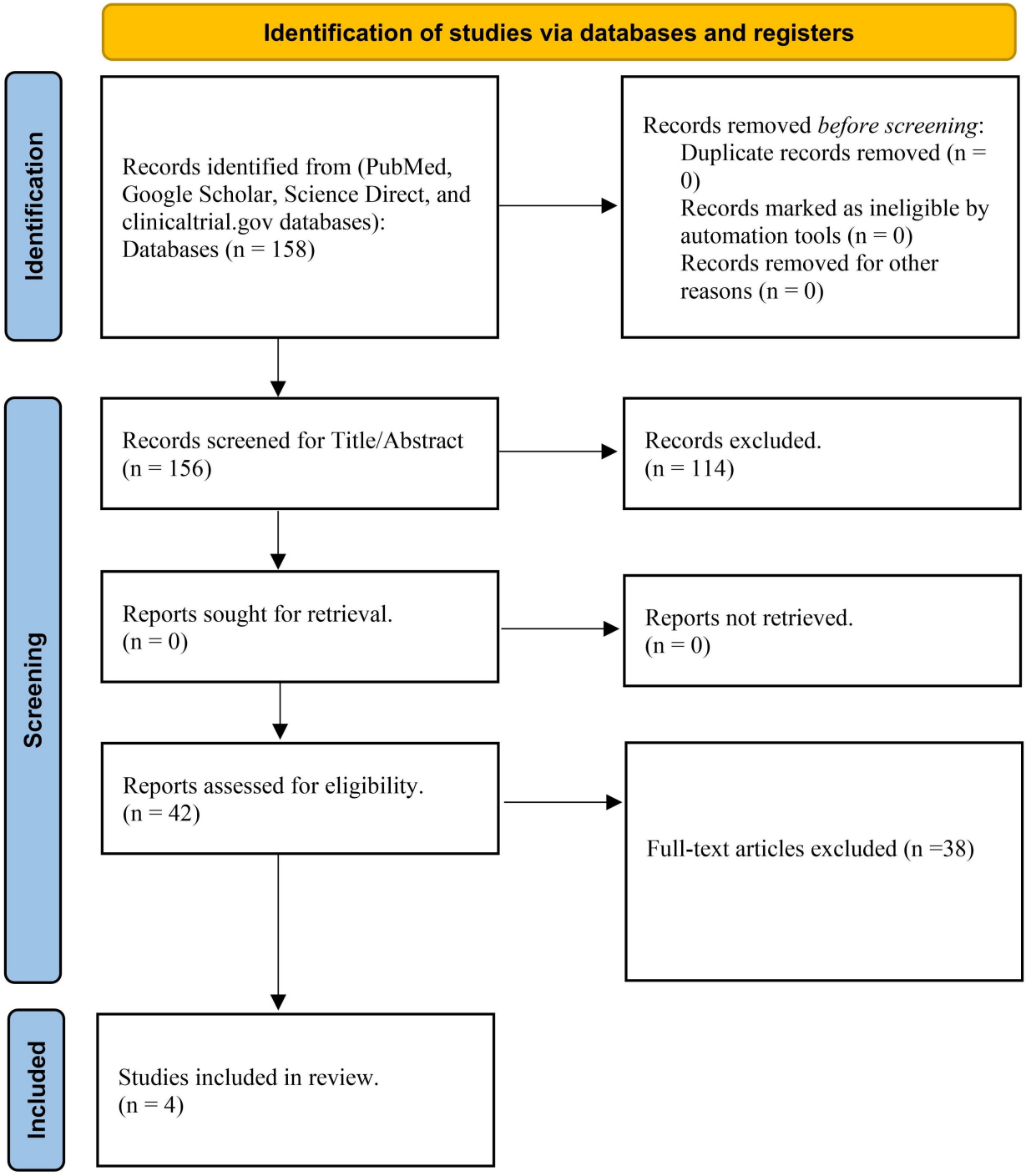

FIGURE 1. PRISMA flow diagram of study selection.

to differentiate into various cell types like smooth muscle, endothelial and nerve cells. Intravenous mesenchymal stem cell injections could replace the damaged endothelium and cavernous smooth muscle cells. Other hypotheses focussed on the paracrine effect where mesenchymal stem cells were produced after the injection as alternative to cellular differentiation. Studies on the application of mesenchymal stem cells and the important mediators in erection mechanism such as intracellular nitric oxide and calcium concentrations had been conducted. The therapeutic goal of SCT in ED was the intracellular regulation of nitric oxide and calcium through various transmembrane transport ionic channels, however, the precise action mechanism was unknown [18].

The four included studies revealed the SCT safety for post-RP ED. No serious adversities were observed in either of the studies. Haahr *et al.* [15] 2016 study exhibited that minimal side effects associated with the liposuction and injection site were documented at one-month assessment but none at the later stages. ADRC were intravenously injected with good tolerability. *Post-hoc* stratification was performed as per the

TABLE 1. Baseline characteristics and quality assessment of included studies using Cochrane Robins I tool.

Study	Sample size	Patients' age/ years Mean ± SD	Study period/ months	Confou-nding	Selec-tion of partic-ipants	Classif-ication of interv-entions	Devi-ation from inter-vention	Missing data	Measu-rement of out-comes	Selection of reported results	Overall
Haahr *et al.* 2018 [14]	21	60.2 Range (46–69)	16	Low	Low	Low	Low	Low	Low	Low	Low
Haahr *et al.* 2016 [15]	17	63 IQR (9)	16	Low	Low	Low	Low	Low	Low	Low	Low
Yiou *et al.* 2015 [12]	12	63.6 ± 4.2	12	Low	Moderate	Low	Low	Low	Low	Low	Low
Yiou *et al.* 2017 [13]	15	59.9 ± 3.8	60	Low	Low	Low	Low	Low	Low	Low	Low

SD: Standard Diviasion.

TABLE 2. Changes in sexual function scores after stem cell treatment.

Study	IIEF score	Baseline	Mo 1	Mo 3	Mo 6	Mo 12
Yiou *et al.* [12] 2015						
	IIEF-IS	3.9 ± 2.5	4.9 ± 2.7	6.7 ± 4.2	6.8 ± 3.6	-
	IIEF-SD	6.7 ± 2.6	6.4 ± 2.1	7.3 ± 1.7	7.5 ± 1.5	-
	IIEF-OS	3.9 ± 2.2	3.2 ± 2.3	5.1 ± 2.9	5.5 ± 2.4	-
	IIEF-EF	7.3 ± 4.5	9.8 ± 8.8	14.6 ± 10.1	17.4 ± 8.9	-
	IIEF-OF	3.5 ± 3.0	4.0 ± 3.8	6.0 ± 3.8	6.3 ± 3.3	-
Yiou *et al.* [13] 2017						
	IIEF-IS	4.6 ± 2.0	4.9 ± 3.1	7.0 ± 4.4	7.2 ± 3.6	6.9 ± 3.4
	IIEF-SD	6.4 ± 2.7	6.2 ± 2.4	7.3 ± 1.6	7.6 ± 1.6	7.6 ± 1.1
	IIEF-OS	3.9 ± 2.3	2.9 ± 2.0	5.0 ± 3.1	5.8 ± 2.3	5.8 ± 2.7
	IIEF-EF	7.1 ± 3.1	10.0 ± 9.8	14.8 ± 10.3	18.4 ± 8.2	18.1 ± 7.0
	IIEF-OF	3.8 ± 3.1	4.0 ± 3.6	5.9 ± 3.4	6.3 ± 2.6	6.0 ± 2.4

EF: erectile function; IIEF: International Index of Erectile Function; IS: intercourse satisfaction; OF: orgasmic function; OS: overall satisfaction; SD: sexual drive; Mo: Month.

status of urinary continence. As a result, 8 of 11 continent men had their EF returned with a mean difference of 0.57 (0.38–0.85; $p = 0.0069$) compared to the included individuals. However, EF was not restored in incontinent males. The improvements in International Index of Erectile Function-5 (IIEF-5) scores and EF demonstrated the safety and efficacy of ADRCs. It was thus considered as a possible interventional therapy for ED after RP [15]. Its follow-up study in 2018 depicted 8 mild reversible events associated with liposuction but no major adverse events. Hence, the intravenous injection of ADRCs was safe as per the phase 1 study with 12-month follow-up [14].

Yiou *et al.* [12] 2015 study demonstrated no serious adverse effects. As per the IIEF-15 and Erection Hardness Scale, substantial improvements in IS and EF domains after six months were reported compared to the baseline in study

TABLE 3. Adverse events reported during and after treatment.

Study	Stem cell type	Adverse events
Haahr *et al.* [14] 2018	ADRC	8 reversible minor events related to the liposuction.
Haahr *et al.* [15] 2016	ADRC	Five patients reported minor events related to the liposuction and ADRC injection at the one-month evaluation time point. Two men had transient redness and swelling at the injection sites, one had a scrotal and penile hematoma that resolved within 14 days, and 2 patients reported abdominal pain and tenderness for 2–6 days after the liposuction. All events resolved without intervention, and at the 3- and 6-month evaluations, no patients reported any side- or adverse events.
Yiou *et al.* [12] 2015	BM-MNC	No serious events reported.
Yiou *et al.* [13] 2017	BM-MNC	No serious events reported.

ADRC: adipose-derived regenerative cells; BM-MNC: bone marrow mononuclear stem cells.

population. Spontaneous erections were noticeably improved with the higher doses. Improvements in peak systolic velocity and penile nitric oxide release tests were linked to the clinical improvements persisting after a year. Penile vascularization and EF improvements were noted [12]. The stage 2 results of this study in 2017 exhibited that EF improvements were comparable to those in stage I with no side effects. The intracavernous BM-MNC injections were thus safe and enhanced EF. The patients receiving 1×10^9 cells reported improved EF after six months [13]. The adverse events reported in the included studies could not be compared with those of the literature because of dearth of studies, which further underscored the importance of future research.

Vakalopoulos *et al.* [19] stated that the usage of stem cells in ED therapy had advanced. However, much was required to be developed as practical and effective therapy alternative for clinical application. The precise way stem cells reacted at injection site, their regenerative effects through differentiation, the paracrine effect, and precise method of their action on many ED forms required explanations and redressals [19]. Gur *et al.* [20] described that RP-related ED might be targeted through cavernous nerve regeneration and vascular healing using SCT. Several challenges must be met before the stem cell-based treatments of ED in clinical settings. The primary action mechanism of SCT for ED was the paracrine activity rather than cellular differentiation. The upcoming clinical trials should involve the intracavernosal injection of single stem cell type [20].

The therapeutic efficacy of trials demonstrated that SCT might be an effective and long-lasting treatment even for severe ED. The differential stem cell populations had revealed milieu-dependent differentiation and functional recovery in ED models. A range of cell-based therapies might thus treat penile vascular dysfunction caused by vasculogenic and neurogenic factors [21].

SCT was a potential alternative for treating ED in cavernous nerve injury rodent models as per the literature on animal studies [6]. However, the clinical studies on humans were lacking and required further research. Stem cells could promote the regeneration and recovery of penile tissue damaged by inflammation and free radicals. To the best of knowledge, this study was among the few published studies on STC's role in post-RP ED. The systematic search methodology and keywords analysis of this field had added to the advantages and strength of this study. Including high-quality studies had further defined the strength of this paper. However, this study had certain limitations. Firstly, the outcomes of this paper could not be generalized because of the inclusion of four heterogeneous, and non-randomized studies with smaller sample size. Further evidence-based clinical research studies were necessary. Secondly, the results of this study could not be compared to other studies due to limited human studies available in literature, which further signified the need of planned research.

5. Conclusion

This study evaluated the role of stem cell therapy (SCT) in post-RP ED. The included studies showed efficacy and safety, however, the current information on SCT for ED was limited. It could still serve as a foundation for future research. Large-scale human studies with robust research designs were necessary for more objective and conclusive evidence pertaining to the translational application of SCT for ED. The studies conducted through clinical randomized controlled trials were imperative for elaborating the outcomes and safety profiles of this novel approach.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

STA—protocol development, data collection; OS—protocol development, manuscript writing, manuscript review; NAA—protocol development, data collection; AE—data analysis, manuscript writing; AI—manuscript review and editing; SMA—protocol development; AMA—protocol development; RA—protocol development; MA—data collection; SAA—data collection; AMA—data collection; ASA—data collection; SA—manuscript review and editing; AAH—manuscript Review and editing; BH—manuscript review and editing; MAA—manuscript review, and editing. All authors contributed to editorial changes in the manuscript.

All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Capogrosso P, Salonia A, Briganti A, Montorsi F. Postprostatectomy erectile dysfunction: a review. The World Journal of Men's Health. 2016; 34: 73.

[2] Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, *et al*. Erectile dysfunction. Nature Reviews Disease Primers. 2016; 2: 16003.

[3] Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. The Journal of Sexual Medicine. 2009; 6: 2538–2546.

[4] Bratu O, Oprea I, Marcu D, Spinu D, Niculae A, Geavlete B, *et al*. Erectile dysfunction post-radical prostatectomy—a challenge for both patient and physician. Journal of Medicine and Life. 2017; 10: 13–18.

[5] Wani MM, Rai BP, Webb WR, Madaan S. Is there a role for stem cell therapy in erectile dysfunction secondary to cavernous nerve injury? Network meta-analysis from animal studies and human trials. Therapeutic Advances in Urology. 2022; 14: 175628722210869.

[6] Mangır N, Türkeri L. Stem cell therapies in post-prostatectomy erectile dysfunction: a critical review. The Canadian Journal of Urology. 2017; 24: 8609–8619.

[7] Asker H, Yilmaz-Oral D, Oztekin CV, Gur S. An update on the current status and future prospects of erectile dysfunction following radical prostatectomy. The Prostate. 2022; 82: 1135–1161.

[8] Protogerou V, Chrysikos D, Karampelias V, Spanidis Y, Sara EB, Troupis T. Erectile dysfunction treatment using stem cells: a review. Medicines. 2021; 8: 2.

[9] Xu P, Wang YH. Prevention and treatment of erectile dysfunction after prostatectomy: an update. National Journal of Andrology. 2017; 23: 656–662. (In Chinese)

[10] Siregar S, Novesar AR, Mustafa A. Application of stem cell in human erectile dysfunction—a systematic review. Research and Reports in Urology. 2022; 14: 379–388.

[11] Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. The BMJ. 2016; 355: i4919.

[12] Yiou R, Hamidou L, Birebent B, Bitari D, Lecorvoisier P, Contremoulins I, *et al*. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. European Urology. 2016; 69: 988–991.

[13] Yiou R, Hamidou L, Birebent B, Bitari D, Le Corvoisier P, Contremoulins I, *et al*. Intracavernous injections of bone marrow mononucleated cells for postradical prostatectomy erectile dysfunction: final results of the INSTIN clinical trial. European Urology Focus. 2017; 3: 643–645.

[14] Haahr MK, Harken Jensen C, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, *et al*. A 12-month follow-up after a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. Urology. 2018; 121: 203.e6–203.e13.

[15] Haahr MK, Jensen CH, Toyserkani NM, Andersen DC, Damkier P, Sørensen JA, *et al*. Safety and potential effect of a single intracavernous injection of autologous adipose-derived regenerative cells in patients with erectile dysfunction following radical prostatectomy: an open-label phase I clinical trial. EBioMedicine. 2016; 5: 204–210.

[16] Hansen ST, Lund M, Ostergaard LD, Lund L. Role of regenerative therapies on erectile dysfunction after radical prostatectomy. International Journal of Impotence Research. 2021; 33: 488–496.

[17] Yiou R. Stem-cell therapy for erectile dysfunction. Bio-Medical Materials and Engineering. 2017; 28: S81–S85.

[18] Pérez-Aizpurua X, Garranzo-Ibarrola M, Simón-Rodríguez C, García-Cardoso JV, Chávez-Roa C, López-Martín L, *et al*. Stem cell therapy for erectile dysfunction: a step towards a future treatment. Life. 2023; 13: 502.

[19] Vakalopoulos I, Memmos D, Mykoniatis I, Toutziaris C, Dimitriadis G. Stem cell therapy in erectile dysfunction: science fiction or realistic treatment option? Hormones. 2018; 17: 315–320.

[20] Gur S, Abdel-Mageed AB, Sikka SC, Hellstrom WJG. Advances in stem cell therapy for erectile dysfunction. Expert Opinion on Biological Therapy. 2018; 18: 1137–1150.

[21] Albersen M, Weyne E, Bivalacqua TJ. Stem cell therapy for erectile dysfunction: progress and future directions. Sexual Medicine Reviews. 2013; 1: 50–64.

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