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REVIEW ARTICLE

Shock Wave Therapy Special Issue

Low-intensity extracorporeal shockwave therapy in the treatment of erectile dysfunction following radical prostatectomy: a critical review

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Abstract

Low-intensity extracorporeal shockwave therapy (LI-ESWT) to the penis has recently emerged as novel therapeutic option in the treatment of erectile dysfunction (ED). Randomized-controlled studies investigating the effect of this new treatment modality revealed promising results in men with vasculogenic ED. However, the efficacy of LI-ESWT in men who develop ED following radical prostatectomy (RP) remains obscure due to the exclusion of this group in nearly all clinical trials. In this review, the authors synthesize the findings from available preclinical and clinical studies that examine the potential utility of LI-ESWT in men with post-RP ED.

Introduction

Prostate cancer is the most commonly diagnosed solid organ malignancy in men. For early localized prostate cancer, radical prostatectomy (RP) using either open or robotic/laparoscopic techniques are widely employed as a first-line treatment option [1]. Although there have been significant advancements in our understanding of the prostate anatomy and the use of minimally invasive surgical techniques, erectile dysfunction (ED) secondary to RP continues to be a common and a challenging problem to manage [1, 2]. Furthermore, despite the advent of nerve-sparing techniques, trauma to the neurovascular bundle (NVB) during RP cannot be completely avoided [1, 2]. It has been reported that the NVB can be compromised by mechanical manipulation, heating, ischemic effects, as well as local inflammation during the procedure. Incidence rates of post-RP ED have been reported between 6 and 68% [1, 2]. Some degree of erectile function (EF) may return spontaneously after RP, however, it may take over 2 years in many cases [1]. Studies have shown that <50% of patients return to baseline EF after surgery despite many receiving treatment with phosphodiesterase type-5 inhibitors (PDE5Is) [2].

The current non-surgical therapeutic options for ED include oral PDE5Is and intracavernous injections with various combinations of vasoactive agents (i.e., alprostadil, papaverine, and phentolamine). These options have been widely used with high rates of effectiveness and are relatively safe with minimal adverse events reported [3, 4]. However, these options do not have any therapeutic effect in patients with impaired blood supply to the corpora cavernosa, and none of these modalities are curative because they do not provide restoration of endothelial or neuronal function [3–6]. As a common result, these treatment options only provide symptomatic relief in select patients. Therefore, the challenge in ED treatment is to develop a modality, which will directly recapulate the cavernosal vasculature, as well as the neuronal function of the penis and improve erectile capacity.

Recently there has been a shift in the focus of ED research from symptomatic treatment toward restorative therapies, notably stem cell therapy, shockwave (SW) therapy, and gene therapy with the aim of existing more durable treatment responses and organic erections without the need for medication [7]. These therapies have been

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explored in animal models, as well as in humans with promising results. However, due to various drawbacks and limitations related to the studies that have explored these techniques (i.e., lack of control group, heterogenous device specifications, and regimens), they are not currently accepted as treatment options for patients outside of a clinical trial setting.

Recent data from several studies suggest that the aim of "long-lasting"and "curative therapy" for ED may be met using low-intensity extracorporeal SW therapy (LI-ESWT) applied to the corpora cavernosa [3–7]. It has been reported that this new therapeutic modality is unique in that it aims to restore EF in order to enable spontaneous erections [3, 4]. Recent studies have shown that LI-ESWT is an emerging approach for ED with a promising treatment efficacy. To date, four meta-analyses have been reported in the literature, and all revealed that LI-ESWT significantly improved EF, as demonstrated by increases in the validated International Index of Erectile Function Questionnaire (IIEF) score. On the other hand, studies related to the efficacy of LI-ESWT are mainly focused on vasculogenic ED, while patients with a history of RP were excluded from almost all clinical trials. Therefore, the usefulness of LI-ESWT in post-RP ED has yet to be determined. However, basic science studies investigating the efficacy of LI-ESWT on neurological disease, as well as ED may help to broaden our understanding related to its clinical potential for post-RP ED.

Scientific background of LI-ESWT

Modern medicine utilizes myriad forms of energy (i.e., thermal, magnetic, and radiation) for diagnostic and therapeutic purposes. Various intensities of longitudinal acoustic waves, also referred to as SWs, have been used for decades to treat a variety of conditions. High-intensity SW therapy has been used to non-invasively fragment urinary calculi, and medium-intensity SW therapy has more recently been used to treat joint pain, tendonitis, and bursitis. LI-ESWT has emerged and quickly gained popularity as a potential treatment for ED, as data from both in vivo and in vitro studies have revealed that these SW can stimulate angiogenesis [8]. The impetus for applying LI-ESWT to the penis came from animal models in which SW therapy was applied to the mycardium of pigs. The results of these experimental models demonstrated that LI-ESWT led to an improvement in ischemia-induced myocardial dysfunction [9]. In light of these results, researchers have postulated that LI-ESWT therapy applied to the corpora cavernosa may improve penile blood flow parameters and endothelial function by stimulating angiogenesis in the penile vasculature.

SWs have two important features for exerting their therapeutic effect: they carry energy, and they are able to propagate through tissue. Studies show that when SWs are non-invasively focused on an organ or tissue, their energy causes a sudden jump to a peak positive acoustic pressure, the "shock", followed by a longer-lasting period of negative pressure. While the biological mechanism of action of SWs on the corpora cavernosa is not fully understood, it has been hypothesized that the targeted tissue is compressed due to the positive acoustic pressure generated by the shock, followed by expansion, which occurs over tensile elements of the tissue [10]. Nishida described this phenomenon as "cavitation" because it can be observed creating micrometer-sized bubbles that violently expand and collapse. The physical forces generated by these cavitation bubbles are highly localized and they induce a localized stress response on endothelial cell membranes secondary to sheering forces. Finally, this shear stress leads to release of angiogenic factors, namely increased production of nitric oxide (NO) through the increased activity of endothelial NO synthase (eNOS) and neuronal NOS (nNOS), platelet-derived growth factor, and vascular endothelial growth factor (VEGF). Additionally, it has also been shown that SWs cause hyperpolarization, activation of the Ras signaling pathway, non-enzymatic synthesis of NO, and upregulation of stress fibers and intercellular gaps [9, 10]. In a recent article, Frey et al. summarized the mechanism of action of SWs and their effects on tissues. Briefly, the authors reported that according to the literature; SW therapy causes neoangiogenesis, recruitment of progenitor cells, modulation of vasodilation, and nerve regeneration in several tissues both in human and experimental animal models [11].

Pathophysiology of post-RP ED

The cavernous nerves that are responsible for organic penile erections run laterally on either side of the prostate in NVBs. As outlined earlier, injury to the NVB can occur regardless of whether nerve-sparing techniques are employed during RP. It has been reported that surgical manipulations including coagulation, traction, and compression near the NVB are the main contributing factors to cavernous nerve neuropraxia [1, 2]. Even temporary NVB injuries can cause to Wallerian degeneration, which results in the denervation of the cavernosal tissue and ultimately loss of EF. In addition to erections, cavernous nerve function also governs physiologic perfusion and oxygenation to the corpora. The long-term sequela of cavernous nerve injury is penile hypoxia, structural remodeling with smooth muscle apoptosis, and eventual veno-occlusive dysfunction. The concept of penile rehabilitation following RP has been

introduced as a means of preventing the aforementioned cascade. Since the Wallerian degeneration process occurs slowly in humans, partial EF recovery is usually observed by 3 months after RP and maximum EF is regained up to 2 years or longer following RP [1, 2].

Experimental studies of LI-ESWT

Several animal models have been used to elucidate the potential mechanisms by which LI-ESWT exerts its therapeutic effect [7]. Wang et al. assessed the biological effect of LI-ESWT in rabbits and found that LI-ESWT induces cell proliferation and increases eNOS and VEGF expression. These angiogenic markers increased within 8 weeks of treatment, and the processes of neovascularization and cell proliferation were durable for >12 weeks following treatment [12]. Chen et al. investigated the changes in cell morphology in healing bones of rats after treatment with LI-ESWT. The results of their study showed that LI-ESWT increased the number of local mesenchymal stem cells, ultimately leading to increased differentiation of osteoblasts and chondrocytes. Additionally, LI-ESWT caused a significant increase in the expression of growth factors such as transforming growth factor-β1 (TGFβ1) and VEGF-A [13]. Furthermore, Nishida and colleagues reported that LI-ESWT significantly increased VEGF in an experimentally induced chronic myocardial ischemia model [9]. The effect of LI-ESWT on erectile physiology has recently been studied by Qiu et al. in diabetes-induced rats. In this model, the investigators revealed the protective effect of LI-ESWT on EF as assessed by improvements in intracavernosal pressure following cavernosal nerve stimulation. In Qiu's study, it was shown that while EF was significantly decreased in all diabetic rats, EF was significantly improved in diabetic rats treated with LI-ESWT. Additionally, the abundance of nNOS-containing nerves, endothelial and smooth muscle cells, and mesenchymal stem cells were significantly higher in the LI-ESWT treated group when compared with controls [14]. Similarly, Assaley-Kaddoum and colleagues investigated the effect of LI-ESWT in a type-2 diabetic rat model using in vivo and in vitro EF assessments. The results of this study showed that LI-ESWT improved EF via a NO/cyclic guanosine monophosphate-independent mechanism [15]. More recently, Jeong et al. conducted a similar study using a diabetic rat model and found that electromagnetic cylinder ESWT treatment resulted in an increase in VEGF, nNOS, and eNOS expression, reduced smooth muscle atrophy, and increased endothelial cell regeneration [16]. Finally, Zhu et al. investigated the mechanism of combination therapy with mesenchymal stem cell therapy (MSCT) in conjuction with LI-ESWT in a diabetic rat model. Their study demonstrated that the ESWT and MSTC combination therapy lead to a synergistic improvement in EF by increased expression of VEGF and consequent phosphoinositide 3-kinase/protein kinase B/ mammalian target of rapamycin pathway signaling [17].

Experimental studies in neural injury/neurological disease models

The effect of LI-ESWT therapy on recovery from neuronal injury has also been a focus of several in vivo studies. It has been reported that the mechanism of LI-ESWT's neuroprotective and/or neuroregenerative effects may stem from attenuation of local inflammation, improved expression of neurotrophic factors, and reduction of free radicals.

Schuh and colleagues examined the effects of LI-ESWT on Schwann cell isolation, culture, and proliferation rate. Schwann cells treated with ESWT had higher proliferative capacities and ability to be isolated and cultured in vitro suggesting enhanced regenerative capacity [18]. This suggests that activation of SC may improve nerve regeneration, but this has not been proven clinically.

In another study, Lee et al. described the effects of LI-ESWT on functional recovery and neurotrophin-3 expression in the spinal cord after sciatic nerve injury in rats. The results of this study showed that early application of SWT increased the expression of neurotrophin-3 and neurotrophin-3 mRNA, and daily SWT caused activation of macrophages and Schwann cells, which are heavily implicated in the survival and regeneration of neurons [19]. Similarly, Chen et al. reported the protective effect of LI-ESWT on peripheral neuropathy in a diabetic mouse model of ED. The authors found that the protective efficacy of LI-ESWT on peripheral nerves occurred through suppression of inflammation and oxidative stress [20]. Hausner et al. conducted a similar study and reported that nerve conduction velocity and amplitude was significantly increased in the LI-ESWT-treated group compared with controls. More importantly, the authors noted the importance of the positive effects of the therapy on regeneration of neurons especially in the initial injury phase [21]. Lobenwein et al. investigated the therapeutic effect of LI-ESWT on motor activity, coordination, and balance deficits in an ischemia-related spinal cord injury model in rats. The authors revealed that LI-ESWT had a protective effect neuronal degeneration via stimulation of Toll-like receptor (TLR)-3, which caused macrophage-modulated inflammation and TLR4 downregulation. Furthermore, it has also been observed in this study that LI-ESWT caused to angiogenesis, which lead ultimately to axonal regeneration after spinal cord injury [22]. In a similar study, Yahata et al. observed that LI-ESWT suppressed cell death and axonal damage by inducing VEGF protein expression in neurons, astrocytes, and oligodendrocytes [23]. When taken together,

LI-ESWT exerts neuroprotective effects in multiple disease models, which supports the notion that it may be of benefit in the setting of RP-induced ED.

Experimental studies in post-RP ED models

Specific to the focus of the current review are animal studies that have examined the effect of LI-ESWT in rat models of cavernosal crush injury. Wang and colleagues reported that LI-ESWT increased brain-derived neurotrophic factor (BDNF) expression in the rat penis after bilateral cavernosal nerve injury (BCNI). Additionally, BDNF expression was found to be increased in Schwann cells in vitro following LI-ESWT [24]. Furthermore, Li et al. conducted a similar experiment using the BCNI model in rats. Rats were divided into four groups: sham surgery, BCNI alone, BCNI followed by treatment with SWs at low energy, and BCNI followed by treatment with SWs at high energy. After SW treatment, EF was assessed with changes in intracavernosal pressure following electrical stimulation, and histological and molecular evaluation of penile tissues. SW therapy was found to improve EF in rats with pelvic neurovascular injury by causing angiogenesis, tissue restoration, and nerve regeneration via recruitment of endogenous progenitor and Schwann cells. LI-ESWT led to more complete re-innervation of penile tissue with regeneration of nNOS+ nerves from the major pelvic ganglia to the penis. In vitro results found that LI-ESWT has a direct effect on promoting Schwann cell proliferation [25]. These results were supported by another study from the same group in which both in vitro and in vivo experiments were performed [26]. Recently, combined therapeutic efficacy of human adipose-derived stem cells (h-ADSCs) applied to injured cavernous nerves in tandem with LI-ESWT to the corpora cavernosa in a rat model of post-prostatectomy ED has been investigated. ADSC and SWT treatment significantly improved EF compared with either ADSC or SWT alone. Furthermore, combination therapy significantly increased alpha smooth muscle actin content, nNOS and eNOS expression in the cavernous nerve, and cyclic guanosine monophosphate (cGMP) production compared with ADSC or SWT alone. The authors concluded that ADSCs mediated recovery of injured cavernous nerves, whereas LI-SWT improved angiogenesis in the cavernosal tissue [27].

Clinical studies using LI-ESWT in men with ED from any etiology

Although there have been several studies evaluating LI-EWST for ED in humans, available data are poor, and results have been mixed. The first study to evaluate the safety and efficacy of LI-ESWT in ED was a single-arm trial that enrolled only patients with vasculogenic ED. This study included 20 men with mild to moderate vasculogenic ED who failed to respond to PDE5I therapy. Patients received LI-ESWT with the Omnispec 1000 device using the following treatment parameters: 1500 shocks per session; energy flux density of 0.09 mJ/mm^2; each cycle consisted of two sessions per week for 3 weeks; two cycles were conducted with 3-week treatment pause in between. At the end of the study, EF was improved in 15 of the 20 men and the mean increase in IIEF-EF score was 7.4. Similarly, all nocturnal penile tumescence parameters improved in the 15 men who responded to LI-ESWT treatment [3]. Following this initial trial, four single-arm studies and five randomized-controlled trials (RCTs) have been conducted.

In another study, 29 men with severe ED were included. In this study, mean IIEF score was found to increase from 8.8 to 12.3 following treatment, an increase that is on the border of a "clinically significant" improvement [4]. During that same year, the authors reported their short-term results of a randomized, double-blinded, sham-controlled study. The authors reported that LI-ESWT has a positive short-term clinical and physiological effect on EF in men who respond to oral PDE5I therapy [5]. In another study, LI-ESWT therapy was effective in improving EF in men with severe ED who are PDE5I nonresponders as well. About half of patients in this study were able to regain the ability to have satisfactory sexual intercourse with the use of PDE5Is after LI-ESWT treatment [6]. In another similar study, Tsai et al. showed that 94.3% of patients who responded to LI-ESWT had durable treatment responses at 3 months follow-up. Thus, LI-ESWT could be considered as a salvage therapy for ED patients who failed to respond to PDE5I's [28]. Importantly, a study from a group in Japan noted that although LI-ESWT seems as an effective treatment option in men with ED, age and comorbidities are negative predictive factors of therapeutic success [29].

In contrast to the aforementioned articles, a more recent double-blind RCT conducted by Fojecki from Denmark investigated the effectiveness of LI-ESWT in 126 men with ED of any etiology and reported that there is no clinically significant effect on EF [30]. Additionally, the same group of investigators noted in another study that two cycles of LI-ESWT for ED were found to be not superior to one cycle at 6 and 12 months follow-up [31]. Another prospective, double-blinded RCT involving 105 men with ED of any etiology found that LI-ESWT slightly improved EF, however, there was no significant difference between the study and placebo groups [32]. Similar to these trials, mixed results have also been reported in regards to the efficacy of ESWT treatment on penile Doppler ultrasonography parameters. While Kalyvianakis et al. confirmed the beneficial effect of LI-ESWT on penile hemodynamics 12 months following treatment, Yamacake et al. reported that

LI-ESWT had no impact in penile Doppler parameters in a subgroup of men with ED associated with end-stage renal disease [33, 34].

To date, there have been four systematic reviews and meta-analyses assessing LI-ESWT for treatment of ED, the most extensive of which was conducted by Lu et al. The analysis included 14 studies involving 833 patients from 2005 to 2015. Seven studies were RCTs, however, there was significant heterogeneity between the setup parameters, device specifications, and treatment protocols in each RCT. This observation supports the importance of developing standardized treatment protocols for each SW machine. Despite these variations, the results of this meta-analysis revealed that men with ED experienced improvements in their ED after LI-ESWT treatment [35]. Additionally, three other meta-analyses and systematic reviews with almost the same number of patients supported the idea that treatment of ED with LI-ESWT resulted in a significant increase in IIEF-EF scores [36–38]. However, these meta-analyses include several RCTs with significant limitations, including one with high dropout rates (~50% in both arms) and another with no robust statistical analysis. Morever, the duration of effectiveness is <12 months highlighting the limitation of this modality in the management of ED. When taken together, the efficacy and more importantly the duration of efficacy of LI-ESWT treatment for men with ED remains undefined. As such, treatment of ED men with this modality has been relegated to controlled clinical studies at little or no costs to patients in some countries (http://www.smsna.org/V1/images/SMSNA_Position_Statement_RE_Restorative_Therapies.pdf).

LI-ESWT as a treatment for men with ED after RP

Despite the large number of patients included in the trials mentioned above, a common exclusion criterion was prior RP. As a result, there is a paucity of evidence examining the efficacy of LI-EWST in patients with post-RP ED.

The first study to target this patient population was conducted by Frey et al. This study included patients who underwent nerve-sparing robotic RP for localized prostate cancer. In this study, patients with no history of pre-operative ED were treated two times per week, every other week for a total of 6 weeks. Each treatment session involved delivery of 1000 SWs with energy flux densities of 20, 15, and 12 mJ/mm^2 applied to the base of the penis, the shaft, and a few millimeters proximal to the glans, respectively, for a total of 3000 SWs at a frequency of 5 Hz. Of note, all patients in this trial had mild to moderate ED after their RP, and LI-ESWT was initiated 1-year post-RP. Treatment efficacy was evaluated using IIEF score at 1 month and 1 year after the last LI-ESWT session. Sixteen patients completed the study, with a median follow-up duration of 24 months. Median IIEF score prior to RP was 25 and decreased to 9.5 postoperatively (prior to LI-ESWT). Following LI-ESWT, the median change in IIEF score was + 3.5 and + 1, at 1-month and 1-year follow-up, respectively. The authors concluded that LI-ESWT may improve EF after nerve-sparing RP, but not to a clinically significant extent. Additionally, there were several limitations in this study, such as the absence of a sham group and the small sample size [11]. In another study, Chung et al. investigated the effect of LI-ESWT in men with ED in an open label single-arm prospective study. Unfortunately, only three patients in this cohort had ED secondary to prior RP. Nonetheless, these patients did not appear to derive significantly greater benefit from LI-ESWT compared with their vasculogenic counterparts [39].

More recently, LI-ESWT has been assessed as an option for penile rehabilitation in 128 men who underwent nerve-sparing cystoprostatectomy due to muscle invasive bladder cancer. Patients in this study were divided into three study groups: LI-ESWT group ($n = 42$), PDE5Is group ($n = 43$), and control group ($n = 43$). All patients of three groups had insufficient EF for sexual intercourse; with decrease in mean IIEF score from 27.9 preoperatively to 6.9 postperatively. Potency recovery rates at 9 months were 76.2, 79.1, and 60.5% in the LI-ESWT, PDE5I, and control groups, respectively. Increases in IIEF and Erection Hardness Scores (EHS) during all follow-up periods in all the groups was found statistically significant, likely due in part to physiologic recovery of EF over time. However, there was no significant difference between the three groups for IIEF and EHS values during the follow-up periods. According to the results of this study, the authors suggested that 16% more patients in the LI-ESWT group had recovery of potency as compared with the control group. Although the difference was not statistically significant, it may be considered as clinically important [40].

In the recent literature, it has also been reported that according to the ClinicalTrials.gov data there are three relevant registered clinical trials evaluating LI-ESWT in post-RP ED, however, none have reached completion. Undoubtly, present clinical data are not robust enough for suggesting LI-ESWT for the routine clinical management of post-RP-related ED, and there is an urgent need for well-designed clinical studies with a larger number of patients [2].

Discussion

RP continues to be the mainstay treatment for localized prostate cancer, however, rates of post-RP ED remain high

despite advances in nerve-sparing techniques. The advent of PDE5Is, vacuum-assisted erection devices, and intracavernosal injection with vasoactive agents was a major advancement in the management of ED, and each may have a role in the treatment of post-RP ED in select patients. However, these modalities provide only symptomatic relief and do not restore a patient's ability to achieve a natural physiologic erection. Furthermore, many patients fail to respond to or cannot tolerate these therapies. As such, research efforts have shifted away from symptomatic relief and focused more on treatments with restorative capabilities. LI-EWST has rapidly emerged as one such potential avenue for restoring natural erections [7]. As outlined above, there are myriad studies in various animal models of disease (diabetic, BCNI, sciatic nerve injury, and myocardial ischemia), which support the ability of LI-ESWT to promote neovascularization, Schwann cell proliferation, nerve regeneration, progenitor stem cell recruitment, and permit increases in intracavernosal pressure following electrical stimulation [14–17, 25–27] However, robust experimental data definitively elucidating the mechanism of LI-EWST is still lacking. Despite encouraging results observed in animal models, the dearth of efficacy data of LI-ESWT in humans, particularly those with post-RP ED, is concerning. The heterogeneity of treatment parameters (dosing frequency, energy flux density settings, number of shocks, linear vs. focused SW device) used in each study also makes comparison and interpretation difficult. As a result, the Food and Drug Administration has not approved any LI-ESWT device for treatment of ED in the United States.

The three studies (two small single-arm studies, one RCT) assessing LI-ESWT in the post-RP setting demonstrated no clinically significant improvement in IIEF (>4-point increase) or EHS scores when compared with placebo. Further, several of these studies were confounded by concomitant use of erectogenic aids during the trial period (as high as 75% in the study conducted by Frey). Additional large-scale RCTs that include this group of patients should be conducted with long-term (2–4 year) follow-up using a validated and standardized protocol, before this modality can be confidently recommended to patients. In 2017, the Sexual Medicine Society of North America released a position statement regarding restorative therapies for ED (LI-ESWT included), urging the medical and scientific community to continue to better understand the mechanisms and clinical benefit of LI-ESWT before offering it to patients. Future studies should continue to be conducted under research protocols in compliance with an Institutional Review Board, and patients should be informed regarding the potential benefits and risks. The position statement also advocates that patients involved in these clinical trials should not incur more than basic research costs for their participation (http://www.smsna.org/V1/images/SMSNA_Position_Statement_RE_Restorative_Therapies.pdf).

Conclusion

LI-ESWT is one of several emerging restorative therapies with the potential to allow for pharmacologically unassisted erections in patients with ED secondary to RP. Experimental studies suggest that LI-ESWT may have a beneficial effect on EF in men with post-RP-related ED by augmenting neoangiogenesis and trophic effects on Schwann cells, synthesizing neurotrophic factors, as well as recruiting and activating progenitor stem cells within cavernosal tissue. Despite these encouraging results, the precise mechanism of action that LI-ESWT exerts remains unknown. Clinical data assessing LI-ESWT for post-RP ED are also limited, as many of these patients were excluded from the initial trials. From current available data, this modality improves EF, but not to a clinically significant extent. To date, there is no level 1 evidence to support the use of LI-ESWT in patients with post-RP ED or ED from any other etiology. As additional well-designed RCTs with long-term follow-up data become available, many of the questions surrounding the use of LI-ESWT in post-RP patients will be answered. This includes but is not limited to: protocol standardization, follow-up time optimization, and efficacy measurement. When taken together, LI-ESWT is a potential restorative therapy for post-RP ED, however, additional preclinical and clinical studies are required before its widespread use.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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