Review Article

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Low-intensity extracorporeal shock wave therapy for erectile dysfunction: Myths and realities

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To review the evidence of clinical efficacy of low-intensity extracorporeal shock wave therapy (Li-ESWT) for the treatment of erectile dysfunction (ED). A search on PubMed using Medical Subject Headings terms [((low intensity extracorporeal shockwave therapy) OR (Li-ESWT)) AND (erectile dysfunction)] was conducted in August 2022, to obtain studies on the use of Li-ESWT for the treatment of ED. Its success rate in terms of International Index of Erectile Function-5 (IIEF-5) score and Erection Hardness Score (EHS) improvement was recorded and analysed. A total of 139 articles were reviewed. Overall, 52 studies were included in the final review. 17 studies were on vasculogenic ED, 5 on post pelvic surgery ED, 4 specifically on ED in diabetic patients, 24 on non-specified origin ED and 2 on mixed pathophysiological origin ED. The mean age of patients was 55.87±7.91 (standard deviation) years and the duration of ED was 4.36±2.08 years. The mean IIEF-5 score went from 12.04±2.67 at baseline to 16.12±5.72, 16.30±3.26 and 16.85±1.63 respectively at 3, 6 and 12 months. The mean EHS went from 2.00±0.46 at baseline to 2.58±0.60, 2.75±0.46 and 2.87±0.16 respectively at 3, 6 and 12 months. Li-ESWT may be a safe and efficacy option for the treatment and cure of ED. Further studies are needed to assess which patients are more suitable for this procedure and which Li-ESWT protocol can lead to the best outcomes.

Keywords: Erectile dysfunction; Extracorporeal shockwave therapy

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for achieving satisfactory sexual performances [1,2]. It is a common disease worldwide, for which a tailored treatment strategy should be used according to invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations [1,3].

As a general premise, ED can be treated successfully with current treatments options, but it cannot be cured, with the potentially exceptions of psychogenic ED, post-traumatic arteriogenic ED in young patients and hormonal causes [1].

Although the oral therapy with phosphodiesterase type 5 inhibitors (PDE5Is) have long been considered the first line of treatment, some patients did not respond or poorly

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respond to this kind of medications; as a result, this led to additional non-surgical treatment options being sought, such as vacuum erection device (VED), intraurethral alprostadil and intracavernosal injections (ICIs) [4].

However, it was showed a consistent discontinuation rate for all these treatment options: 4.4% to 76% for PDE5I, 18.6% to 79.9% for ICI, 32% to 69.2% for urethral suppositories, and 50% to 64% for VED [1].

In recent years, low-intensity extracorporeal shock wave therapy (Li-ESWT) has been suggested as a promising treatment for vasculogenic ED, being the only currently available treatment that could provide a cure, which is the most desired outcome for most men suffering from ED [1,5-12].

The healing rationale is the documented effect of this acoustic waves in inducing cellular pathways that increase the expression of local growth factors, improving endothelial function, angiogenesis, and perhaps even regeneration of nerve fibers [12-15].

Moreover, following the first reporting of Li-ESWT in the treatment of ED by Vardi et al. [9] in 2010, several studies have evaluated the efficacy of Li-ESWT in different pathways of ED, either organic (vasculogenic or neurogenic) or mixed [10-63]. The patients included in the studies show significant differences as regard cardiovascular risk factors, response to PDE5I, duration and severity of ED [1].

Furthermore, there is a wide heterogeneity among shockwave generators, type of shockwaves emitted, setting parameters, and treatment protocols used [1].

Against the background of this heterogeneous data, it is indeed difficult to establish across the board whether Li-ESWT is a viable option for the management of ED. To acquire evidence on the myths and the realities of the efficacy of Li-ESWT for the treatment of ED, we reviewed the available literature considering the achievable outcomes when applied to different patients, erectile disfunction aetiologies and protocols.

MATERIALS AND METHODS

1. Search strategy

We performed a search of PubMed database to investigate the current studies on Li-ESWT for patients with ED. The search terms were [((low intensity extracorporeal shockwave therapy) OR (Li-ESWT)) AND (erectile dysfunction)].

2. Inclusion and exclusion criteria

Titles and abstracts were examined, and manuscripts were classified. Randomized clinical trials, retrospective, prospective, and comparative studies on human man affecting by ED and treated with Li-ESWT were included in the review. Case reports, commentaries, letters to the editor, reviews, and non-English literature were excluded a priori. Full-text assessment was performed for the remaining articles with the same inclusion/exclusion criteria.

1) Characteristics of the patients

Participants were diagnosed as having ED according to European Guideline diagnostic criteria.

In light of the purpose of our review, there were no limitations on ethnicity, age, comorbidity and cardiovascular risk factors. Moreover, no restrictions were placed on PDE5I consumption during the Li-ESWT treatment period or after and on the duration and severity of ED.

According to this, we evaluated the following baseline characteristics of the patients: mean age, diagnosis of diabetes mellitus, smokers or ex ones, response to PDE5I, duration and stage of ED.

2) Li-ESWT protocol

We analysed the Li-ESWT protocols used in different studies, especially the duration and the total number of the treatments, the shocks per treatment, the shocks delivered for patient, the energy flux density (EFD) and the type of generators. We included studies in which patients could use PDE5I during the treatment; on the contrary we excluded the analyses on combination of Li-ESWT and other surgical and non-surgical therapies for ED. All types of shockwaves emitted, setting parameters, and treatment protocols were included, as well as all the different shockwave generators.

3) Outcomes

To evaluate the safety and efficacy of Li-ESWT in the management of ED we analysed the following main outcomes: International Index of Erectile Function-5 (IIEF-5) score, Erection Hardness Score (EHS), peak systolic velocity (PSV) on penile Doppler ultrasonography and the occurrence of adverse events. Moreover, any follow-up (FU) protocol was reported in this review.

3. Data handling and extraction

According to the predefined criteria, two independent authors (ACB and MP) evaluated and extracted data from papers. During the process of data extraction, disagreements were resolved through discussion with a third investigator (AC).

4. Statistical analysis

A pooled analysis was performed, and all collected data were evaluated using Statistical Package for Statistical Sciences, version 25.0 (IBM SPSS Corp.).

RESULTS

Of 139 records identified by database searching, a total of 52 studies have been finally included in this review. A flow diagram for study screening and selection is shown in Fig. 1. All the included studies were published between 2012 and 2022. Thirty-nine studies were randomized controlled trials (RCTs), of which 9 compared Li-ESWT versus sham treatment in the management of ED. We included 17 studies on vasculogenic ED, 5 studies on post pelvic surgery ED, 4 studies specifically on ED in diabetic patients, 24 studies on non-specified origin ED and 2 studies on mixed pathophysiological origin ED (1 on ED in kidney transplanted patients and 1 on ED due to priapism). In all the studies the FU was no longer than 12 months.

An overview of main data extracted are shown in the Supplementary Table.

Pooled mean age of patients was 55.87±7.91 years and pooled mean duration of ED was 4.36±2.08 years.

As concerning the characteristics of Li-ESWT, the pooled mean of number of shocks per treatment was 3,230±2,138, the pooled mean of total number of shocks was 26,310±18,324 and the pooled EFD was 0.01±0.03 mJ/mm^2. Analyzing the baseline characteristics of the patients, the pooled mean IIEF-5 was 12.04±2.67 while the pooled mean EHS was 2.00±0.46.

Pooled characteristics of patients and of Li-ESWT protocols are shown in Table 1.

After treatment, the pooled IIEF-5 at 3 months was 16.12±5.72, the pooled IIEF-5 at 6 months was 16.30±3.26 and the pooled IIEF-5 at 12 months was 16.85±1.63.

After treatment, the pooled EHS at 3 months was 2.58±0.60, the pooled EHS at 6 months was 2.75±0.46 and the pooled EHS at 12 months was 2.87±0.16.

The pooled IIEF-5 and EHS at baseline and at 3-6-12 months of FU are resumed by Table 2 and their improved scores from baseline are showed in Figs. 2, 3, respectively.

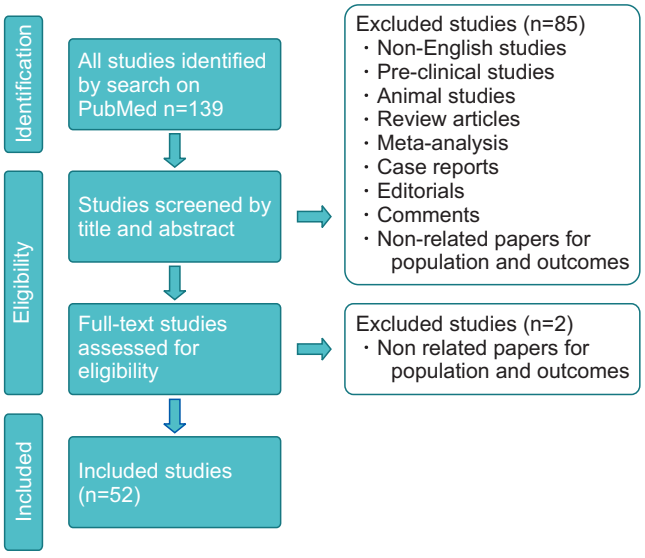

Fig. 1. Flowchart for study selection.

Table 1. Pooled characteristics of patients and of Li-ESWT protocols

Characteristic	Mean±standard deviation
Age (y)	55.87±7.91
Duration of erectile dysfunction (y)	4.36±2.08
Shocks per treatment	3,230±2,138
Total number of shocks	26,310±18,324
Energy flux density (mJ/mm^2)	0.01±0.03

Li-ESWT, low-intensity extracorporeal shock wave therapy.

Table 2. Outcomes of the pooled IIEF-5 and EHS at baseline and at 3-6-12 months of FU

	IIEF-5	EHS
Baseline	12.04±2.67	2.00±0.46
3 mo FU	16.12±5.72	2.58±0.60
6 mo FU	16.30±3.26	2.75±0.46
12 mo FU	16.85±1.63	2.87±0.16

Values are presented as mean±standard deviation.
FU, follow-up; IIEF-5, International Index of Erectile Function-5; EHS, Erection Hardness Score.

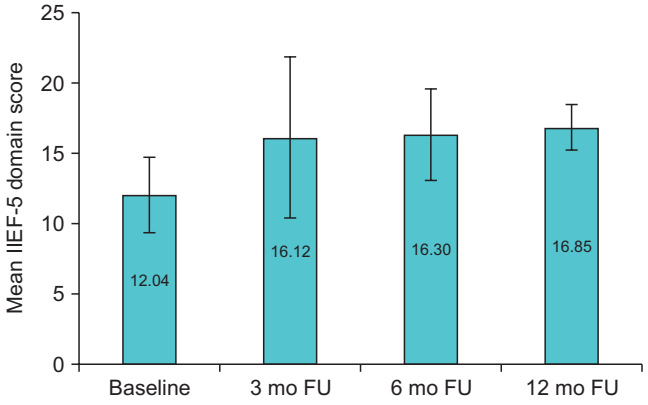

Fig. 2. Change from baseline in International Index of Erectile Function-5 (IIEF-5) domain score. FU, follow-up.

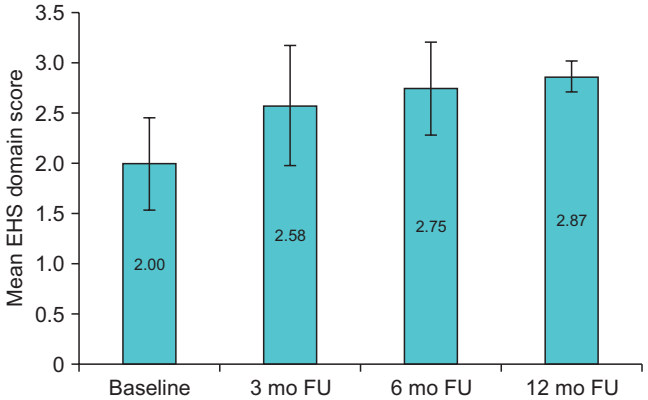

Fig. 3. Change from baseline in Erection Hardness Score (EHS) domain score. FU, follow-up.

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DISCUSSION

Approximatively 30% of man >40 years old experience ED, and the prevalence further increases with age [1,2]. This condition can affect considerably the quality of life of men and their partners [3].

A variety of surgical and no-surgical therapies are available, including oral PDE5I, vacuum pumps, intraurethral medications, ICIs, and penile prosthesis [14,64]. However, none of these treatments can cure the underlying pathology and adverse effects, complications, or loss of sexual spontaneousness are common causes of elevated rates of discontinuation and dissatisfaction [14]. In recent years, Li-ESWT has emerged as a promising approach for ED's treatment and cure and many publications on this topic have been released since 2010 [1,9].

Li-ESWT is a non-invasive technique that uses the targeted passing of acoustic waves through tissues to induce a stress effect [14]. On the whole, the shockwaves exert stress on tissues through two main mechanisms: the first is direct mechanical stress associated with the high-amplitude shockwave, and the second ones is correlated to the growth and violent collapse of cavitation bubbles in fluid [14]. The impact of cavitation is most likely to cause lesions within the blood vessels than surrounding tissue, as a bubble surrounded by tissue will be bound by it that will not allow it to pass through a cycle of violent growth and collapse [14]. Microbubbles, derived from bubbles implosion, cause disruption of the endothelium in vascularization and tissues can result in neoangiogenesis (by activation of resident stem cells with chemokine production attracting progenitor endothelial cells and release of VEGF) [2,65]. In addition, microbubble collapse induces shear stress and could simulate endothelial production of nitric oxide. Finally, shockwave therapy might also enhance Schwann-cell-mediated nitrergic-nerve repair after injury [14]. However, the exact mechanism of action of Li-ESWT for ED is not yet fully known, such as factors affecting the treatment success.

The effect of low-intensity shock waves has been studied *in vitro* models and in animal, in order to determine the mechanisms that can lead to a clinical improvement in patients with ED. For instance, in 2013 Qiu et al. [66] reported a positive effect of Li-ESWT on regeneration of nerves, endothelium and smooth muscle in diabetic rat models; later, Li et al. [67] demonstrated that angiogenesis, tissue and nerve generation can be promoted by this procedure in rats with pelvic neurovascular injuries. Also, in 2016 a review by Pan et al. [68] led to hypothesize that the shockwave-induced microtrauma and the subsequent angiogenic neovascularization resulted in an improvement in penile blood flow. Numerous systematic reviews and meta-analyses have been conducted to validate Li-ESWT for treatment of ED in human, although the heterogeneity of variables evaluated in literature is wide.

Above all, there is a broad heterogeneousness among shockwave generators (electrohydraulic, electromagnetic, piezoelectric, and electropneumatic), type of shockwaves emitted (focused, linear, semi-focused, and unfocused) setting parameters (EFD and number of pulses per session), and treatment protocols (duration of treatment, sessions number per week, total number of shockwave pulses delivered, and penile sites of application) [1]. All this results in a different influence on the shape and amplitude of the waves and their effects on tissues.

As regards the protocol, there is no standardized one and for instance, different authors reported a total number of treatments between 4 and 12 and a total number of shocks delivered between 6,000 and 80,000 with a variable EFD from 0.05 to 0.25 mJ/mm^2.

Furthermore, several clinical studies have evaluated the changes that Li-ESWT can determine in patients with different comorbidities, risk factors and affected by distinct etiopathogenesis of ED. In 2012, Gruenwald et al. [12] demonstrated a significant improvement in IIEF-ED score in patients with severe ED that poorly responded to PDE5I. In a meta-analysis Lu et al. [69] patients with mild ED at baseline were shown to benefit most from Li-ESWT, whereas Yee et al. [16] highlighted the positive effect of Li-ESWT on both IIEF-ED score and EHS score when applied to patients with mild-moderate to severe ED, in a double-blinded placebo-controlled trial [5]. Later, a recent RCT conducted by Ortac et al. [52] a good impact on mild vasculogenic ED in young patients has been obtained with Li-ESWT compared to placebo in a RCT. Studies on Li-ESWT as a treatment for ED in diabetic patients have led to different outcomes. On one side, clinical amelioration have been reported in the RCT by Shendy et al. [45] and in the comparative study between Li-ESWT plus tadalafil vs tadalafil alone by Verze et al. [36]; on the other ones, no significant changes have been evidenced by Ergün and Akyüz [63] on diabetic patients with severe ED.

Regarding the penile rehabilitation after pelvic surgery, the efficacy of Li-ESWT is still controversial. If two studies on the use of Li-ESWT for ED following radical prostatectomy and cystectomy have led to significant improvement in the IIEF score [28,51], other ones on ED after nerve-sparing robot-assisted radical prostatectomy have reported just a slight improvement [19,43]. Regarding the various Li-ESWT

protocols, Kalyvianakis et al. [33] have highlighted that better sexual performances can be achieved by increasing the number of treatments, and consequently the total amount of shocks delivered [6]. In addition, they suggested that patients may also benefit equally when the same number of treatments is applied with a different frequency (in terms of number of treatments per week), whereas a higher EFD can yield better results [33]. In this review, we summarized the main outcomes obtained with the use of Li-ESWT in distinct populations and with various Li-ESWT protocols. Despite the evaluation of the changes in PSV can provide objective data on the efficacy of Li-ESWT, just few studies reported this variable, so that was excluded from our results. Rather, we focused on two subjective outcomes that are widely explored in most of the studies: the change in the IIEF-5 score and EHS from baseline.

The pooled IIEF-5 score at three months (16.12±5.72) after the procedure compared with baseline (12.04±2.67), it suggests that Li-ESWT can induce a fast and effective result on the sexual function, which lasts up to twelve months (16.85±1.63). As regards EHS, compared to the baseline value (2.00±0.46) the improvement achieved at 3 months (2.58±0.60), tends to increase at six (2.75±0.46) and twelve months. (2.87±0.16). The increase of EHS in the short term appears more evident than the one of IIEF-5 score. The reason could be that the treatment rapidly allows to reach a greater penile hardness, but it improves less significantly the ability to maintain the erection in the first months.

Regarding the adverse events of Li-ESWT, only few studies have reported low grade complications, such as headache, dizziness, dyspepsia, local penile pain, fatigue and mild fever. This suggests the safety of the procedure.

The result of this review indicates that Li-ESWT can be a valid option in the wide range of treatments for ED, especially in patients who poorly respond to oral medications and who are unwilling to face more invasive procedures. Surely, further studies are needed to understand which patients may mostly benefit from treatment and which protocol it can give the best outcomes.

This review has some limits: most of the studies included small sample sizes and did not analyse objective outcomes, and the FU was relatively short. Moreover, comorbidities, different aetiology of ED, the variety of protocols and machines, and variable use of PDE5I during the treatment can add more confounding factors.

CONCLUSIONS

This review aims to assess the efficacy of Li-ESWT for the treatment of ED. The IIEF-5 score and EHS improved in patients who underwent the procedure with results maintained at 12 months of FU, highlighting the effectiveness of this treatment. Moreover, only few studies have reported low grade complications, suggesting the safety of the procedure. Additional studies are needed to explore the relationship between the aetiology and the severity of ED and the efficacy of Li-ESWT. Finally, a further effort must be directed to establish a standardized protocol for the shock waves delivery.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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None.

AUTHORS' CONTRIBUTIONS

Research conception and design: Alessia Celeste Bocchino. Data acquisition: Alessia Celeste Bocchino and Marta Pezzoli. Statistical analysis: Arturo Lo Giudice and Giorgio Ivan Russo. Data analysis and interpretation: Arturo Lo Giudice and Giorgio Ivan Russo. Drafting of the manuscript: Alessia Celeste Bocchino and Marta Pezzoli. Critical revision of the manuscript: Andrea Cocci and Juan Ignacio Martínez-Salamanca. Supervision: Andrea Cocci. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Supplementary Table can be found via https://doi.org/10.4111/icu.20220327.

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