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Low-intensity extracorporeal shock wave therapy in the treatment of erectile dysfunction. Diagnostic and therapeutic options — a literature review

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Abstract

Low-intensity extracorporeal shock wave therapy (Li-ESWT) is a modern therapeutic option for erectile dysfunction (ED). The European Association of Urology (EAU) has classified it as a first-line treatment for ED. The use of Li-ESWT is recommended in appropriately informed patients with mild erectile dysfunction (EF). The recommendations include the use of LI-ESWT for patients who respond poorly to drug therapy and those who, for individual reasons, are unable or unwilling to use vasoactive substances. It is worth noting that the level of recommendation is described as weak (insufficient evidence of efficacy, indicating the need for further research). The mechanism of action of Li-ESWT is not well understood, but it is known that it affects the formation of new blood vessels, promotes quantitative and qualitative improvement of vascular endothelial cells, and increases the production of nitric oxide (has a nutritional effect, generating congestion). Improvement of erectile function in people undergoing Li-ESWT was noted in patients with vascular ED, and importantly, studies are underway to apply this form of therapy to other etiopathogenesis of ED. Li-ESWT results in an improvement in EF as measured by the International Index of Erectile Function (IIEF), an increase in the average Erectile Hardness Score (EHS), and an improvement in quality of sexual life; however, the level of increase remains clinically unsatisfactory. The efficacy of Li-ESWT has been confirmed in studies in patients with the most advanced vascular ED. Importantly, there were no side effects both during and after therapy and the improvement in EF was sustained long-term (up to 2 years). The advantages of Li-ESWT therapy are associated with the removal of the cause of vasogenic ED, which transfers into improved sexual performance, allows patients to regain spontaneity of intercourse and prompts wider use of this innovative therapy.

Keywords: low intensity shock wave therapy, angiogenesis, vascular erectile dysfunction, international index of erectile function, erectile hardness score, penile doppler ultrasound

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Erectile dysfunction

According to the definition provided by the National Institutes of Health (NIH), erectile dysfunction (ED) involves sexual problems which manifest mainly by the loss of erection and ejaculation despite the presence of sexual arousal in men [1]. Temporary erectile dysfunction shall not be confused with permanent ED, as the latter most often results from poor blood supply to the penile region. ED is a condition in which the penis fails to achieve or maintain a full and lasting erection, which impedes penetration and other sexual activities. Studies show that 50% of men aged 40 to 60 years struggle with erectile dysfunction and many of them underestimate this problem and decide to give up sexu-

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al activity, based on the conviction that ED is a natural occurrence foreshadowing the onset of andropause [2]. Erectile dysfunction causes patients to experience low self-esteem, depression, and fear of being rejected by a partner, leading to avoidance of sexual stimulation [3]. Owing to recent advances in medical technologies, novel treatment methods are now available and help patients return to former sexual activity, therefore increasing their self-esteem and improving mental health. Guidelines published by the European Association of Urology (EAU) in 2021, [4] recommend phosphodiesterase type 5 inhibitors (PDE5I) as first-line therapy for ED. If no or poor effectiveness of the PDE5I therapy is observed, vacuum erection devices (VED) remain an acceptable second-line therapy, while low-intensity extracorporeal shock wave therapy (Li-ESWT) has been suggested as a promising treatment option for properly informed patients with vasculogenic ED.

The science behind Li-ESWT

The Li-ESWT works by the emission of mechanical waves which propagate faster than acoustic waves [5] and are characterized by high amplitude, lack of periodicity, and the ability to achieve high, short-lasting peak pressure. There is a rapid increase in pressure applied on the treated tissue followed by a decrease in negative pressure values (from –10 to 100 MPa) [6].

Despite well-described clinical effects of Li-ESWT, the exact underlying mechanism of its biological action remains unknown. However, numerous scientific reports have already addressed this issue and hypothetical mechanisms of Li-ESWT interaction have been presented. Many authors who document the use of Li-ESWT in ED believe that shockwaves may activate the release of angiogenic factors, which promote the development of blood vessels, therefore improving blood supply to the affected tissue. Nishida et al. [7] observed that the application of Li-ESWT led to a significant mRNA overexpression of strong angiogenic ligands (stimulation of endothelial cell proliferation), expression of proteins in the human umbilical vein endothelial cells (in vitro) and significant improvement in regional blood flow through the myocardium (Li-ESWT was applied in 200 impulses to each of 9 different sites; 0.09 mJ/mm^2, research on pigs — *in vivo*). Based on these findings, two possible mechanisms of action have been described: 1) enzymatic, involving the increase in activity of endothelial nitric oxide synthase (eNOS) [8] and 2) non-enzymatic, requiring the presence of L-arginine and hydrogen peroxide molecules [9].

The improvement of blood flow allows to eliminate pathological processes directly related to the ischemia in cavernous bodies, which involve the increase in synthesis of endothelin-1 and collagen, a decrease in the synthesis of collagenase enzymes and promotion of apoptosis of smooth muscle cells in the trabeculae of cavernous bodies (which impair normal blood flow) [10].

Penis anatomy

The penis can be anatomically divided into three basic elements: 1) two cylinder-shaped corpora cavernosa, arranged symmetrically on both sides of the penis in its upper part and constituting the vast majority of the entire penile surface; they originate from the perineum, running to the base of the glans and joining in the middle of the penis shaft; they fill with blood during penile erection, allowing for sexual intercourse and promoting changes both in the length and volume of the penis; 2) one corpus spongiosum located in the lower region of the penis, which is soft and easily compressible, enabling the adaptation of its shape to corpora cavernosa, therefore ensuring perfect conditions for both erection and ejaculation; the urethra, which also functions as the vas deferens, runs through the corpus spongiosum [11]. These anatomical elements of the penis stay closely connected by a common layer of connective tissue (penile fascia). It is also worth noting that the internal morphological elements of the penis are surrounded by the tunica albuginea, consisting of rather tightly packed collagen fibers, which may also be subject to injury [12].

Moreover, three segments may be distinguished in the structure of the penis: 1) the root: attached to the anterior pelvic wall by fusion of tunica albuginea surrounding both corpora cavernosa (invisible on the outside), the root itself is immobile but helps keep the entire penis in the right position; 2) the shaft: the longest part of the penis covered with layers of fascia and skin on the outside (this element of the penis has the ability to increase its volume); 3) glans: with acorn-like shape, it is covered with a thin and delicate layer of skin (foreskin), the outer layer of which is always moist, aiding in the insertion of the penis into the vagina during intercourse [13].

The average flaccid penis size is between 7 and 10 cm in length and 8 cm in girth. During erection, the penis increases its length by an average of 30% as compared to the flaccid state, while its girth increases by about 2 cm (these numbers vary depending on the population examined) [14].

Li-ESWT methodology in ED

Considering the above-described anatomy of the penis, the sites commonly subjected to Li-ESWT in men suffering from ED seem to be rational targets for therapy focused on regaining sexual function (Fig. 1).

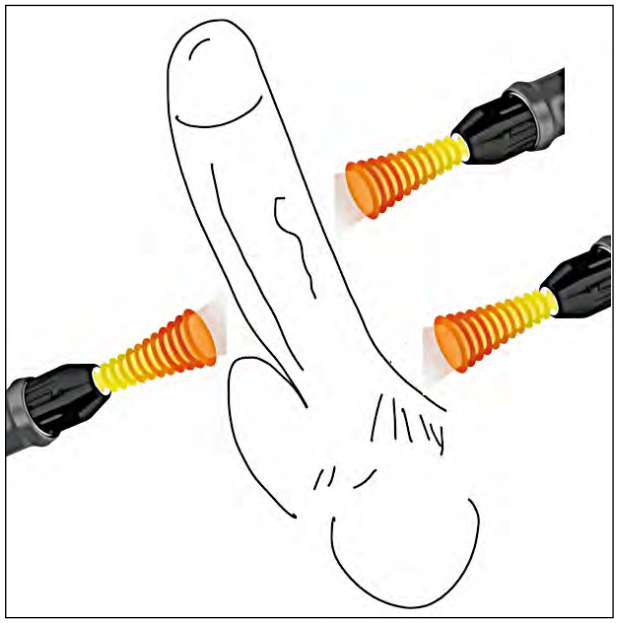

Figure 1. Li-ESWT application sites in the penile region of men suffering from ED (own source)

Current scientific reports lack consistent guidelines regarding the conduction of Li-ESWT, although a lot of attention has been drawn to the parameters of the procedure. However, the method of Li-ESWT implementation and parameter settings may differ significantly depending on the device and clinical experience of a particular facility/healthcare professional [15]. In line with current recommendations and international standards, the model of therapeutic procedure proposed in our study involves performing a series of 6–8 treatment sessions in 7- to 10-day intervals, which allows clinicians to accompany the patient in the process of physiological blood vessel formation in real time and observe the first effects of Li-ESWT which are most frequently reported one month after commencing therapy [16]. The treatment should be carried out in conditions comfortable for the patient, ensuring dignity and safety, without third parties' involvement. Treatment parameters are always selected individually, based on the results of preliminary treatment qualification and possible comorbidities. It is worth emphasizing that the procedure should be painless and its duration depends on the selected parameters, taking approximately 20 minutes [17].

Li-ESWT procedure parameters and devices

Depending on a way the shockwave is generated (ESWT, extracorporeal shock wave therapy), waves may be divided into focused (FSWT, focused shock wave therapy), radial (RSWT, radial shock wave therapy) and, much less frequently used, planar (PSWT, planar shock wave therapy) [18, 19]. A great advantage of the Li-ESWT method is the possibility to precisely apply and focus the energy beam on a targeted treatment site (affected by a disease or pathologically changed), therefore protecting the adjacent tissues [20].

Li-ESWT creates the opportunity to choose between three energy sources: electromagnetic, electro-hydraulic and piezoelectric. However, regardless of the mechanism in which a wave is generated, its biological effect depends on the amount of energy released, making the energy flux density (the rate of energy transferred per unit surface area, expressed in mJ/mm^2) the most important therapeutic parameter [21]. Based on the amount of released energy, ESWT may further be divided into low-intense — Li-ESWT (< 0.2 mJ/mm^2) and high-intense — Hi-ESWT (> 0.2 mJ/mm^2). Some authors suggest 0.28 mJ/mm^2 as a cut-off value for these two types of therapy [22]. Although current data proves that better therapeutic effects are observed with Li-ESWT [21], recent studies show that focused treatment protocols and increasing the energy may produce better results [23]. ED therapy involves the use of Li-ESWT.

While numerous devices are used in ED therapy, it is important to note that the available literature of the subject does not recommend any particular models, which was brought to our attention in 2018 on the 20th Congress of the European Society for Sexual Medicine (CESSM), as well as on the 21st World Congress of the International Society for Sexual Medicine (WMISSM, World Meeting of the International Society for Sexual Medicine) [24]. Porst et al. [23], studied the effectiveness of Li-ESWT in ED (a literature review covering all preclinical and clinical studies published at that time) by analyzing six types of Li-ESWT devices, which differed significantly in terms of generated power (0.09–0.55 mJ/mm^2). What is interesting, the research team documented that positive therapeutic effects have been achieved with all examined devices, even despite significant differences in treatment parameters and high variability of treatment protocols.

Evaluation of therapeutic effects

A wide range of diagnostic tools may be used to verify the quality of a given treatment. The primary tools involve subjective methods, i.e., they are based on individual feelings of a patient [25]. Further exploration of therapeutic effects should be carried out with objective methods, that is, measurements presenting numerical values which may be compared with results reported by

Table 1. IIEF-5 questionnaire used to assess and verify the effects of ED treatment

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low (1 pts)	Low (2 pts)	Moderate (3 pts)	High (4 pts)	Very high (5 pts)
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never (1 pts)	A few times (much less than half the time) (2 pts)	Sometimes (about half the time) (3 pts)	Most times (much more than half the time) (4 pts)	Almost always/always (5 pts)
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Extremely difficult (1 pts)	Very difficult (2 pts)	Difficult (3 pts)	Slightly difficult (4 pts)	Not difficult (5 pts)
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Almost never/ never (1 pts)	A few times (much less than half the time) (2 pts)	Sometimes (about half the time) (3 pts)	Most times (much more than half the time) (4 pts)	Almost always/always (5 pts)
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ /never (1 pts)	A few times (much less than half the time) (2 pts)	Sometimes (about half the time) (3 pts)	Most times (much more than half the time) (4 pts)	Almost always/always (5 pts)

IIEF-5 scoring: The IIEF-5 score is the sum of the ordinal responses to the 5 items.
22–25: No erectile dysfunction
17–21: Mild erectile dysfunction
12–16: Mild to moderate erectile dysfunction
8–11: Moderate erectile dysfunction
5–7: Severe erectile dysfunction

other researchers. Subjective methods of ED evaluation are considered to be all questionnaires examining the improvement of sexual intercourse quality, the size of the erected penis, and the improvement in psychophysical comfort of patients. Objective methods in this field include all imaging and numerical tests which are able to demonstrate the morphological character of the condition, are measurable and repeatable, and give precise results. Conclusions from data analysis should serve as a foundation for reliable assessment carried out by institutions which publish opinions or recommendations and determine therapeutic indications [26]. Having searched through all widely available studies on the implementation of Li-ESWT in ED published in Medline, Embase, PubMed, and Google Scholar online databases, 25 peer-reviewed studies were selected for analysis: 7 meta-analyses and 18 trials, including 12 randomized controlled trials (RCT). The studies were reviewed in terms of therapeutic protocols, doses, procedure effectiveness, and limitations resulting from the adopted methodology — the results are presented below.

Subjective methods for evaluating the effectiveness of Li-ESWT in men with ED

International Index of Erectile Function (IIEF)

The international index of erectile function (IIEF) is a gold standard for assessing ED. This questionnaire was developed while conducting clinical trials with sildenafil — a substance from the PDE5I group (phosphodiesterase type 5 inhibitors), belonging to a new generation of drugs introduced in ED treatment — in order to verify and evaluate the effects of pharmacological treatment. IIEF is a reliable assessment tool which has demonstrated its efficacy in many different populations of patients and has been implemented for final assessment in clinical trials on ED [27]. The most frequently used version of this questionnaire is its abbreviated form, IIEF-5, which meets the psychometric criteria of reliability and validity of the test, presents high sensitivity and specificity, and is compatible with other methods of clinical assessment for patients suffering from ED. The IIEF-5 consists of 5 questions, each of them scored from 0 to 5 (where '0' is assigned to the most severe state of the disorder and '5' means normal function/no disorder). Therefore, the possible total score ranges from 0 to 25 points. Cases of ED analyzed with the use of IIEF-5 were classified into five categories: severe (5–7 points), moderate (8–11 points), mild-moderate (i.e., between 'mild' and 'moderate') (12–16 points), mild (17–21 points) and no erectile dysfunction (22–25 points). The IIEF-5 form (Tab. 1) [28] used in our study is presented below.

One of the first studies using IIEF was conducted by Gruenwald et al. [29]. The authors analyzed 29 patients aged 41–79 years (average age: 61.3 years) with a 60-month median duration of ED. The average IIEF value before treatment (lasting 9 weeks) was 8.8 points, and a month after its completion a significant increase in IIEF score to 12.3 points was observed (at that time, the patients were no longer on pharmacological

treatment). After another month of observation (when the patients were being administered PDE5i), further increase in IIEF score to 18.8 points was noted. In 22 men (75.9%) an increase in IIEF by more than 5 points was reported, while another 8 men (27.6%) declared that all symptoms of ED resolved (IIEF > 25 points). The participants of this study observed improvement in erectile function after an average time of 3 weeks from the date the treatment was commenced (that is, between the 6th and 8th treatment session). A total number of 300 impulses were used, with a frequency of 2 Hz and energy flux density of 0.09 mJ/mm^2. None of the participants reported pain or any other side effects. However, it is important to note that the study was conducted on a relatively small group of patients.

Subsequently, in 2015 and 2016, Bechara et al. [30] evaluated the long-term efficacy and safety of Li-ESWT method on 40 patients (average age: 64.8 years) with vasculogenic ED who had a history of failed therapy with vasoactive substances. Positive response to Li-ESWT was observed in 24 (60%) patients. In this group, the IIEF-5 score increased from 14.8 points up to 24.1 points on average after 3 months of treatment and continued to rise after 6, 9, and 12 months after treatment completion (respectively: 24.3 points, 23.2 points, and 23.9 points). The beneficial effect of Li-ESWT lasted for a year.

Another study conducted by the same research team [31] on a small group of men (n = 20, average age: 63) with a history of poor response to pharmacotherapy involved the application of 20,000 impulses during a 4-week study period. During each session, patients received 5,000 impulses with energy flux density of 0.09 mJ/mm^2. One month after the end of Li-ESWT, the average IIEF-5 score increased significantly ($p < 0.05$) from 14.9 points to 18.2 points. After 3 months, a further slight increase to 19.7 points was recorded. Positive response to Li-ESWT was observed in 60% of patients who completed the therapeutic process (n = 12). The study also pointed out the need to continue research in this field on larger groups of patients. No adverse effects were reported on.

The study conducted by Pelayo-Nieto et al. [32] involved 15 male participants (average age: 59.6 years) with mild (40% of participants) to moderate (60% of participants) ED. A statistically significant improvement in IIEF score was demonstrated in 80% of patients, with a significant average increase from 14.23 points to 19.69 points. A total number of 5000 impulses with energy flux density of 0.09 mJ/mm^2 were applied. However, limitations of the study included a small treatment group and the lack of a control group.

Ruffo et al. [33] examined 31 patients (average age: 59.93 ± 12.16 years) suffering from ED and recorded a significant improvement in the mean IIEF score after one month of treatment. Positive changes in the analyzed parameters maintained up to 3 months after completion of the therapeutic process. The average IIEF score after this period increased to 21 points ($p = 0.0096$) as compared to the initial state evaluated at 16.5 points. Each time, a total number of 3600 impulses with energy flux density of 0.09 mJ/mm^2 were applied, 900 impulses per each anatomical region of the penis. The authors confirmed the effectiveness of the Li-ESWT method and reported the absence of any side effects.

Palmieri et al. [34] conducted a large, multicenter trial on a group of patients (n = 109) with vasculogenic ED who had a history of no response to pharmacological treatment. The Li-ESWT procedures were performed in an outpatient setting with the use of the following settings: 3000 impulses with an energy flux density of 0.25 mJ/mm^2 and a frequency of 4–6 Hz, applied twice a week for 3 weeks. Treatment efficacy was assessed based on the IIEF and EHS questionnaires, as well as in penile Doppler ultrasound. A total number of 97.2% of patients successfully completed treatment and reported on a follow-up visit after 4 weeks. The IIEF score increased significantly by 8.6 points in 75 patients (mean: 13.47 ± 4.61 points vs. 22.07 ± 5.27 points; $p < 0.0001$).

Another paper published by Verze P. et al. [35] is a retrospective study carried out on a large group (n = 156) of patients suffering from ED and type II diabetes, divided into two equal groups. All patients from the treatment group (A, n = 78) received tadalafil (5 mg/day for 12 weeks) combined with Li-ESWT (for 3 weeks), while participants from the control group (B, n = 78) were only given pharmacotherapy (PDE5I). Moreover, patients from the treatment group were further assigned to subgroups (1, 2, 3) which differed in the number of Li-ESWT impulses applied in each session: 1500 (A1), 1800 (A2), and 2400 (A3), respectively. Average changes from the initial IIEF-5 score were evaluated at months 1, 3, and 6 after treatment completion. A significant improvement in the average IIEF-5 score was observed in all groups and subgroups after one month of follow-up. After 3 and 6 months of follow-up, the mean improvement in IIEF-5 was seen to be significantly greater among participants from the A3 subgroup, +5.0 ± 2.1 ($p < 0.001$) and +4.7 ± 2.3 ($p < 0.001$), respectively. This observation suggests the beneficial effect of using more Li-ESWT impulses in the treatment of vasculogenic ED. The study also emphasized a high level of safety of this form of treatment and the beneficial effect of combining pharmacotherapy with LI-ESWT.

Much less optimistic results are those presented by Fojecki et al. [36], who performed Li-ESWT (planar

Table 2. Erection Hardness Scale (EHS) used for subjective assessment of erection

How would you rate the hardness of your erection?
0: Penis does not enlarge
1: Penis is larger but not hard
2: Penis is hard but enough for penetration
3: Penis is hard enough for penetration but not completly hard
4: Penis is completly hard and fully rigid

mode) on a large group (n = 126) of men suffering from ED (all with initial IIEF-5 score of < 25 points). The study participants were randomly divided into two groups: treatment (n = 63) and control (n = 63; sham control). At the beginning of the study, the average IIEF score was 10.9 points in the treatment group and 11.5 points in the control group. At four weeks following the completion of the first 5-week treatment cycle, an increase in IIEF score was observed (up to 13.1 points in the study group and 13 points in the control group), while another 4-week observation period after completion of the next treatment cycle presented a decrease in IIEF (up to 11.8 points in the treatment group and 12.6 points in the control group). Analysis of erectile function did not show any significant differences in terms of treatment efficacy between the two groups, as measured by success rates (37.9% vs. 38.3%; p = 0.902).

On the other hand, a study published by Sramkowa et al. [37] analyzed 60 patients suffering from ED and divided them randomly into two groups: treatment and control. Statistically significantly better results were recorded in the treatment group at 4 and 12 weeks of follow-up after treatment completion (p = 0.049 and p < 0.001, respectively). The control group received sham treatment. Overall, the treatment protocol involved 4 sessions and its effectiveness was evaluated with the use of the IIEF-5 questionnaire. Unfortunately, no other details referring to the therapeutic protocol were provided.

Research conducted by Ladegardy et al. [38] aimed to evaluate the effect of Li-ESWT in the treatment of ED in men who underwent a nerve-sparing prostatectomy and reported IIEF-5 score below 22 points. The study participants were randomly assigned to the treatment group (n = 20) or the control group (n = 18). Each group received one session of treatment per week. A significant increase in the IIEF-5 score in the study group was observed at both 4 and 12 weeks of follow-up after treatment completion. After 12 weeks, the average IIEF-5 score increased by 3.45 points (p = 0.026) in the treatment group. The authors of this study emphasized the need to conduct further clinical trials on larger groups of patients.

Vinay et al. [39] presented the results of a randomized, double-blind study conducted on 76 patients suffering from vasculogenic ED and responding poorly to pharmacotherapy: 40 men were treated with Li-ESWT (1 session/week for 4 weeks; 5000 impulses/session; energy flux density of 0.09mJ/mm^2), while the remaining 36 participants were assigned to sham control. When treatment was completed, the median change in the IIEF-5 score in the study and control groups was 3.5 and –0.5, respectively (p < 0.05). No adverse events were reported in the course of the study. This research demonstrated that Li-ESWT electromagnetic therapy can contribute to a slight improvement in erectile function in some patients who do not respond to PDE5I pharmacotherapy, making it an alternative therapeutic option for properly informed patients suffering from vasculogenic ED who do not consent to more invasive forms of treatment.

Erection Hardness Scale (EHS)

Another commonly used questionnaire for evaluating the effects of ED treatment is a subjective assessment with the use of the erection hardness scale (EHS), scored from 0 to 4, where "0" denotes a complete lack of penis enlargement and '4' describes a completely hard and fully rigid penis (Tab. 2) [40].

An important fact is that the results obtained with IIEF-5 and EHS assessment tools correlate with each other, which makes them useful in evaluating a patient's clinical condition [40]. They are also the most widely-used tools in assessing the effects of ED therapy.

A study published by Gruenwald et al. [29] analyzed a small group of men suffering from ED (n = 29; the number of patients who completed the entire course of treatment, average age=51.3 years) and defined the inclusion criteria by low erection hardness (EHS < 2) during PDE5I therapy. After a month of treatment with Li-ESWT, 10 patients (34.5%) reported an increase in EHS scores (> 3) which allowed them to have sexual intercourse. The implemented therapy involved the administration of 300 impulses with energy flux density of 0.09 mJ/mm^2 and a frequency of 2 Hz.

Interesting results documented by EHS were obtained by Palmieri et al. [34] in a group of 106 patients (97.2% of patients were qualified for the study) treated with Li-ESWT due to ED and not responding to pharmacotherapy. After 4 weeks, 72 (67.9%) of all treated patients reported EHS ≥ 3 (i.e., penis rigidity sufficient for complete sexual intercourse); thirty-seven (34.9%) patients reported EHS = 4 (i.e., fully rigid penis). The treatment protocol involved the administration of 3000 impulses with an energy flux density of 0.25 mJ/mm^2 and a frequency of 4–6 Hz, applied twice every week.

Fojecki et al. [36] found no statistically significant differences in EHS among patients with ED treated with Li-ESWT (planar wave) or receiving sham therapy (3.5%

vs. 6.7%; p = 0.369), as observed immediately after treatment completion and after the next 6 and 12 months of follow-up. Moreover, no differences between patients who received 1 or 2 cycles of Li-ESWT were recorded.

The EHS scale was also implemented by Sramkowa et al. [37] to assess the effects of Li-ESWT in 60 men with ED, who were randomly divided into two groups: treatment (Li-ESWT intervention) and control (placebo). The authors noted a significant increase in EHS in 4 and 12 weeks after treatment completion (p = 0.030 and p < 0.001, respectively), as compared to the sham control group.

Ladegarda et al. [38] have also applied the EHS assessment tool to evaluate the effects of Li-ESWT (5 treatment sessions applied once a week) in 38 men with ED who underwent radical prostatectomy and were divided into two groups: treatment (n = 20) and control (n = 18). In 12 weeks after treatment completion, the average EHS score increased by 0.5 points. (p = 0.019) as compared to the control group. The authors of the study concluded that such a level of increase does not constitute a clinically satisfying result and further research involving larger groups of patients is still required in this field.

Vinay et al. [39] examined 76 patients suffering from ED and obtained the following results 6 weeks after treatment completion: 52.5% (21/40) of patients from the treatment group (Li-ESWT: 1 session/week for 4 weeks; 5000 impulses in each session with an energy flux density of 0.09 mJ/mm^2) and 27.8% (10/36) in the control group (sham/placebo) demonstrated EHS > 2 (p < 0.05). No adverse events were observed in the course of the study. The authors emphasized that Li-ESWT may serve as an alternative treatment option for patients who do not consent to more invasive therapies and may also be introduced as an effective adjuvant ED treatment for properly informed patients presenting with erectile function disorders.

Objective methods for evaluating the effectiveness of Li-ESWT in men with ED

Subjective assessment tools are found to be not sufficient in the reliable evaluation of the therapeutic effects of Li-ESWT in men struggling with ED. Imaging studies were therefore implemented to help visualize the nature of the problem. i.e., impaired blood flow through the penis. The most widely-used tests include penile Doppler ultrasound (PDU).

Penile Doppler Ultrasound (PDU)

PDU involves the examination of arterial blood flow and possible venous outflow from the penile region before and after injection of an erectile function stimulant. This method provides valuable information about the physiology behind penile erection. An ultrasound device equipped with a high-frequency linear transducer (7.5–12 MHz) is used to conduct this examination. Pharmacological agents (usually prostaglandins E1) are injected into the corpora cavernosa with a needle (size 27–30 G, length 12 mm) [41]. Audiovisual materials are allowed to help achieve sexual arousal (AVSS, audiovisual sexual stimulation). The penis is then examined in several projections in order to assess the homogeneity of corpora cavernosa and identify any possible tissue thickenings, fibrosis, or calcification in the penile region, as well as to exclude mechanical damage to penile tissues. The adjacent structures are also subject to ultrasound evaluation. Injection of erection stimulants increases blood flow to the penis by several times and full erection is usually achieved after about 15–25 minutes. That is when a healthcare professional performing the examination can identify the cavernous bodies and blood vessels with an ultrasound probe, which allows for a precise determination of their course and measuring the speed of blood flow in their lumen. In most cases, a pharmacologically induced erection does not cause any discomfort and disappears spontaneously in about 45 minutes [42].

Peak systolic velocity (PSV) is considered a good parameter for assessing the functioning of blood vessels supplying the penis. It should be stressed that, in case of pharmacologically induced erection, PSV > 30 cm/s indicates normal arterial blood flow, while PSV < 25 cm/s denotes arterial insufficiency as the cause of ED. The end-diastolic velocity (EDV), along with the resistive index (RI) provides information about proper functioning of venous outflow mechanisms. In case of normal arterial functioning, EDV > 6 cm/s and RI < 0.6 indicate the presence of a penile venous leak. Abnormal EDV values are most commonly observed with coexisting arteriovenous fistulas, penile venous leak, or fibrosis in the tunica albuginea [26].

Many authors have reported the implementation of PDUs for clinical assessment of therapeutic effects in patients undergoing Li-ESWT. The studies carried out by Kalyvianakis et al. [43] included 46 men with documented vasculogenic ED which had been present for at least 6 months, with an IIEF score of 6–21 points and after a 4-week period of discontinuation of erectile dysfunction pharmacotherapy. The study excluded patients with a history of prostatectomy, presenting with anatomical defects of the penis, undergoing hormone therapy, suffering from psychotic disorders, and those with a history of serious cardiovascular events. Patients were assigned to treatment (n = 30; Li-ESWT) and control (n = 16; placebo) groups, as the

study was a double-blind trial. The treatment protocol involved 12 treatment sessions and the assessment was carried out 3 months after its completion. A significant increase in PSV by 4.5 ($p < 0.001$) was recorded in the treatment group and a PSV increase by 0.6 ($p = 0.45$) was observed in the control group, while the RI was 0.04 ($p < 0.001$) in the treatment group and 0.01 ($p = 0.75$) in the control group. The authors therefore confirmed the safety of Li-ESWT therapy in patients with vasculogenic ED, as no pain or other side effects were reported. A small number of participants and strict inclusion criteria, which are sometimes difficult to meet in clinical practice, were the two important limitations of the presented study.

Similarly, Palmieri et al. [34] discovered that introducing Li-ESWT for patients suffering from ED (who did not respond to PDE5I therapy) can significantly increase the mean PSV (27.79 ± 5.50 vs. 41.66 ± 8.59; $p < 0.0001$), while at the same time decreasing the mean EDV (5.66 ± 2.03 vs. 1.93 ± 2.11; $p < 0.0001$). A clinically significant alteration in penile hemodynamics has been observed in patients with vascular ED.

De Olivier et al. [44] have also demonstrated that Li-ESWT is an effective treatment method for ED. Patients were evaluated with the use IIEF-5 (filled in at the beginning of treatment, then 6 weeks and 3 months after treatment completion), as well as on PDU examination (performed prior to commencing treatment and 6 weeks after its completion). The participants were divided into two groups according to the duration of ED symptoms: less than 2 years ($n = 13$) and more than 2 years ($n = 12$). Initially, PSV was measured to be 29.3 ± 13.0 cm/s, while 6 weeks after Li-ESWT completion its value increased to 35.9 ± 15.2 cm/s ($p = 0.001$). The average baseline EDV was 2.6 ± 4.8 cm/s and it decreased to 1.3 ± 4.3 cm/s ($p = 0.015$) 6 weeks after treatment completion. No statistically significant difference between the two analyzed groups was observed and no adverse events were reported, therefore confirming the safety of this therapeutic option. Moreover, the authors have put forward a thesis that the duration of ED does not affect Li-ESWT treatment results.

A study designed by Yamacke et al. [45] was aimed at exploring the effectiveness of Li-ESWT treatment of ED in 20 men (average age: 53.7 years) after kidney transplantation, who were divided into two groups: treatment group ($n = 10$; Li-ESWT) and control group ($n = 10$; sham/placebo). The Li-ESWT therapeutic protocol involved the application of 2 treatment sessions per week, for 3 weeks (a total number of 6 treatments). The sham control group received therapeutic intervention with the same device as the treatment group, but no energy was generated in the process. Participants were then assessed with the use of the IIEF-5 questionnaire prior to commencing therapy, as well as at months 1, 4, and 12 after treatment completion. Furthermore, all participants underwent penile Doppler ultrasound examination before and after their treatment. Both groups presented similar results prior to beginning therapy. No significant differences between the two groups were observed on PDU examinations conducted before and after treatment. As indicated by the authors, a small number of study participants constitute a significant limitation of this publication.

In their study, Carneiro et al. [46] formulated a hypothesis that AVSS improves PDU accuracy. Their study included 40 men (average age: 61.8 ± 10.2 years) diagnosed with ED. The PDU protocol was chosen randomly: session A featured intracavernous injection (ICI) of a combination of erection-stimulating drugs (papaverine, regitine, and prostaglandin E1) alone, whereas session B involved a combination of ICI and AVSS. The researchers introduced a 7-day interval between the sessions. Patients were examined 4 times: at 5, 10, 15, and 20 minutes after ICI (the following parameters were evaluated: PSV, EDV, and RI). The obtained measurements were then compared both with and without AVSS. In session A, AVSS was implemented in 23 cases (out of 40 participants) and a significant improvement in EDV and RI was observed in this group ($p = 0.022$ and 0.019), as compared to the remaining 17 patients who did not use AVSS. Introducing AVSS did not affect the differentiation of PSV among the two study groups ($p = 0.768$). What is also interesting, the use of AVSS allowed to change the primary clinical diagnosis in 10% of patients. As many as 3 out of 12 patients (25%) diagnosed with penile venous leak (based on PDU without AVSS) were considered to be healthy after AVSS was introduced during PDU examination. Moreover, 1 in 4 patients primarily diagnosed with arterial insufficiency (observed in PDU without AVSS) was considered to be healthy when visual stimulation was added during PDU. The authors therefore concluded that the introduction of AVSS during PDU examination not only improves the response to ICI, but also aids in the proper interpretation of penile hemodynamics.

Shendy et al. [47] conducted a study to investigate the effectiveness of Li-ESWT in treating patients suffering from ED, diabetes, and reporting symptoms of polyneuropathy (confirmed by nerve conduction velocity tests and Doppler ultrasound). Their study included 42 patients aged 41–55 years, who were randomly assigned to one of two groups: treatment group ($n = 21$; Li-ESWT combined with pelvic floor muscle training) and control group ($n = 21$; pelvic floor muscle training and sham Li-ESWT intervention). PDU examination

was applied to assess blood perfusion. Ultrasound evaluation was carried out prior to starting treatment and 3 months after its completion. A significant increase in PSV was observed in both groups. However, clinical improvement after administered treatment was found to be significantly higher in the treatment group when compared to the control group ($p < 0.001$; in both penile arteries) after a 3-month follow-up period.

Flow-Mediated Dilation (FMD)

Both the functioning of the vascular endothelium and its improvement parameters may be monitored by analyzing the degree of artery dilation after its occlusion (FMD, flow-mediated dilation). This safe and non-invasive marker has been implemented in cardiology for predicting cardiovascular events [48]. FMD has also been used to evaluate the clinical effects of Li-ESWT in men suffering from ED.

A study published by Vardi et al. [49] examined 20 men between 33 and 73 years of age (average age: 56.1 ± 10.7 years) diagnosed with vasculogenic ED which lasted for an average period of 35 months. Treatment protocol involved the administration of 2 Li-ESWT sessions a week, for 3 weeks. The whole regimen was then repeated after one month (a total number of procedures: $2 \times 6 = 12$ treatment sessions). Patients were evaluated one month after the end of therapy. The functioning of vascular endothelium in the treatment group was assessed by analyzing the degree of dilation in the dorsal artery of the penis after it had been compressed. The control group underwent ultrasound examination of blood flow in arteries of the upper limb. The basal flow through the above-mentioned artery increased significantly in the treatment group both at rest (7.3 mL/min/dL vs. 17.8 mL/min/dL; $p < 0.001$) and after a 5-minute occlusion (12.0 mL/min/dL vs. 28.9 mL/min/dL, $p < 0.001$). Six months after treatment completion, 10 patients ($n = 10$) reported the presence of spontaneous erections. No changes in blood flow were observed in the control group. Moreover, a correlation between the changes in erectile function and changes in penile vascular endothelial parameters was observed, as evaluated one month after treatment completion. Unfortunately, it once more needs to be emphasized that the promising results of this study should be treated with caution due to a small number of study participants.

Vardi et al. [50] carried out research which demonstrated that Li-ESWT has a positive impact on erectile function in men diagnosed with ED who are at risk of cardiovascular diseases (CVD). The exclusion criteria were defined as follows: anatomical defects of the penis, status post radical prostatectomy, history of pelvic radiotherapy, and current hormonal, psychiatric, or neurological treatment. The patients who qualified for the study were advised to discontinue pharmacotherapy 4 weeks prior to the first Li-ESWT procedure. Study participants ($n = 67$) were randomly assigned to two groups during the preliminary consultation: the treatment group (scheduled to receive a 9-week Li-ESWT) and the control group (sham treatment with the use of identical devices emitting the same sounds as the original Li-ESWT). The preliminary consultation also involved acquainting the patients with basic questionnaires assessing EF and FMD (in the arteries of the penis). Patients treated with Li-ESWT were observed to develop significant changes in hemodynamics in the arteries of the penis in terms of maximum blood flow at rest and after occlusion (8.2 vs. 0.1 mL/min/dL; $p = 0.0001$), whereas no significant differences were recorded in the control group. These results confirm the beneficial short-term clinical effects of Li-ESWT intervention and prove its positive physiological impact on the structure of blood vessels in patients suffering from ED. Although the study was a double-blinded trial, this information should be treated with caution, as with all the studies investigating the effects of Li-ESWT, since the application of a real Li-ESWT device generates vibration clearly felt by the person performing the procedure.

In a study published by Inoue et al. [51], 12 patients with severe ED after radical prostatectomy were found to have a significant improvement of FMD in the arteries of the penis one month after completion of Li-ESWT treatment ($p = 0.0032$) (13.8 ± 1.3 vs. 24.0 ± 2.5 min/dL). What is also important, none of the patients reported any adverse effects. The duration of each Li-ESWT session (consisting of 1500 impulses applied at a frequency of 2 Hz, with an energy flux density of 0.09 mJ/mm^2) was approximately 20 minutes.

Meta-analyses regarding Li-ESWT in ED

Over the years, numerous meta-analyses discussing the use of Li-ESWT in ED have been published. In addition to studies conducted on patients suffering from vasculogenic ED, some authors also evaluated the efficacy of Li-ESWT in men diagnosed with ED who underwent radical prostatectomy, suffered from chronic pelvic pain, presented with penile curvature, and did not respond to pharmacological treatment.

Ayala et al. [52] analyzed the data obtained from a total number of 710 patients treated with Li-ESWT, 439 (61.8%) of whom were also receiving pharmacotherapy (PDE5i) at the same time. In their result analysis the authors did not pay special attention to the type of therapy their patients received (which could contribute

to identifying possible additional benefits of combining different treatment methods) but rather focused on the overall improvement of EF in EHS (which occurred in 43.1% of patients) and on the increase in the number of patients who experienced spontaneous erections and were therefore able to have vaginal intercourse (44% vs. 26.8% prior to treatment; $p < 0.0001$).

The analysis carried out by Kałka et al. [15], who concentrated primarily on patients with CVD and/or CVD risk factors, documented that Li-ESWT is a highly useful method in this group of patients who additionally suffer from ED. The authors of the above-mentioned meta-analysis agree that the introduction of Li-ESWT in ED treatment brings positive effects by significantly increasing the EF score in subjective assessments, while maintaining a high level of safety non-invasive character of the method.

Nevertheless, the authors also emphasize that most of these observations are short-term ones, which creates the need for conducting further research on larger groups of patients and carrying out more detailed analyses of collected data.

A publication prepared by Campbella et al. [53] attempted to collect and summarize the data obtained from numerous RCTs and studies, as well as from previous meta-analyses. Seven RCTs were qualified for analysis with a total number of 607 patients whose IIEF and EHS results were compared. However, the authors indicate significant limitations of this literature review, both in terms of quantity and quality of collected data, especially due to the heterogeneity of groups and unclear descriptions of Li-ESWT treatment protocols used in the available literature (the frequency of treatment sessions, energy flux density, number of administered impulses, the type of shockwave and the device generating the impulses). Despite these limitations, the authors believe the Li-ESWT to be a non-invasive and harmless treatment option which may provide short-term support for patients with vasculogenic ED.

Capogrosso et al. [26] conducted an analysis of available literature from the Medline and Embase databases regarding the effectiveness of Li-ESWT in ED treatment, in order to develop recommendations for the European Society for Sexual Medicine. A total number of 11 RCTs and 5 meta-analyses were qualified for literature review. Cumulative analysis of the available data demonstrated that Li-ESWT is a safe method of ED treatment with an overall positive effect on EF improvement. However, the authors stressed that the effectiveness of Li-ESWT should be considered questionable for the time being, as it requires further research conducted on larger groups of patients.

Along with his research team, Liang Dong [54] investigated numerous databases to find RCTs which examine the use of Li-ESWT in ED. Seven RCTs (published between January 2010 and June 2018) were included in the analysis, involving a total number of 522 patients diagnosed with ED. This literature review documented that men with ED who underwent Li-ESWT reported a significant improvement in terms of average IIEF score as compared to the sham control group ($p < 0.0001$). A significant increase in EHS (OR: 16.02; 95% CI [7.93; 32.37] among patients treated with Li-ESWT was reported in 4 out of 7 analyzed studies ($p < 0.00001$). Moreover, the authors observed that patients with moderate and/or severe ED respond better to Li-ESWT therapy (evaluated with the use of IIEF and EHS). The authors found Li-ESWT to be an effective and safe therapeutic option for ED treatment but they also point out the deficiencies and ambiguities in the description of treatment parameters.

Bochchino et al. [55] conducted a meta-analysis of data from the PubMed database, identifying 139 articles referring to the application of Li-ESWT in ED. Out of this number, 52 publications were included in the final analysis: 17 studies on vasculogenic ED, 4 papers carried out on patients with ED and diabetes, 5 studies focusing on ED in patients after pelvic floor surgery, and 26 papers on ED of undetermined cause. The studies were evaluated for improvements in the IIEF-5 and EHS. The average age of study participants was 55.87 ± 7.91 years and the duration of ED was 4.36 ± 2.08 years. The average IIEF-5 index was 12.04 ± 2.67 points prior to commencing the study, then the IIEF-5 increased to an average of 16.12 ± 5.72 points in 3 months after treatment completion, while at 6 months follow-up from the date the treatment was started the IIEF-5 continued to rise to 16.30 ± 3.26 points and reached 16.85 ± 1.63 points after one year of observation. The EHS score amounted to 2.00 ± 0.46 points at the beginning of the study, then after 3 months of treatment the EHS increased to 2.58 ± 0.60 points, continued to rise up to 2.75 ± 0.46 points after 6 months (erection hardness enabling sexual intercourse), and finally reached 2.87 ± 0.16 points after one year of observation (erection hardness enabling sexual intercourse). The authors concluded that Li-ESWT is a safe and effective alternative for patients with ED but further research is required to standardize and objectify therapeutic protocols.

Yao et al. [56] analyzed 16 RCTs which focused on the use of Li-ESWT in ED treatment, including a total number of 1064 patients. The study participants were evaluated with the use of EHS and IIEF-5 questionnaires. Statistically significant improvement in IIEF-5 score was observed after 1 month [mean difference (MD) = 3.18, 95% confidence interval (CI) = (1.38, 4.98), $p = 0.0005$], 3 months [MD = 3.01, 95% CI = (2.04, 3.98), p

< 0.00001] and 6 months [MD = 3.20, 95% CI = (2.49; 3.92), p < 0.00001] after completion of therapeutic process. The authors point out that the greatest clinical improvement expressed by IIEF score is observed in people with moderate EF disorders. The authors of the presented literature review also recorded an improvement in EF expressed by EHS [odds ratio (OR) = 5.07, 95% CI = (1.78, 14.44) p = 0.002]. It is worth noticing that, in the context of previous considerations, the authors of this meta-analysis concluded that the most favorable results in men suffering from ED are achieved with the use of Li-ESWT energy flux density of 0.09mJ/ /mm^2 and by applying 1500–2000 impulses during one treatment session.

Sighinolfi et al. [57] analyzed the available literature investigating the beneficial effect of Li-ESWT on patients with ED after radical prostatectomy. The author searched through the PubMed and WEB of Science databases (non-English papers, editorial letters, case reports, and reviews were not taken into account; GRADE guidelines were used to avoid systematic errors). Nine publications were qualified for further analysis. Most of the studies included in this meta-analysis focused on comparing the effects of PDE5I in monotherapy with the effects of PDE5I administered in combination with Li-ESWT. The major limitations of this literature review include a small number of studies included in the analysis and the fact that the studies were mostly small and heterogeneous. The limitations described above should be kept in mind when interpreting the conclusions drawn by the authors of this study, who stated that the role of Li-ESWT is limited in the treatment of patients suffering from ED.

Conclusions

Recent scientific reports regarding the implementation of Li-ESWT in treating men who struggle with ED raise cautious optimism and give hope to a large group of patients who are directly affected by this problem. Li--EWST may serve as an alternative treatment option for ED in properly informed patients. The effect of Li-ESWT is causal and has been documented in numerous studies, although it should be noted that these studies are relatively few and are conducted on small groups of patients. Since the most common causes of ED include vascular changes, current lifestyle patterns (improper nutrition, smoking, poor diet, and stress) contribute to the impairment of blood vessel function, which makes ED a social problem with an ever-widening range, affecting younger generations of men [58].

Implementation of Li-ESWT in the treatment of ED fits well into the innovative trends of modern medicine, which investigates the causes of ailments and uses them as treatment targets. What is important, Li-ESWT is a safe and non-invasive method — none of the studies presented above reported any complications after Li-ESWT procedures were performed on patients with ED [15, 23, 26, 54, 56]. In addition, it should be emphasized that Li-ESWT allows patients to restore the ability to have spontaneous sexual intercourse, which is a significant psychological factor [59].

This study aimed to present the basics of Li-ESWT operation, discuss technical solutions used in the treatment of ED, and to review selected papers which assess the effectiveness and safety of Li-ESWT. We hope that this publication will contribute to popularizing this form of ED treatment and will encourage scientists to plan more research in this field.

Article information

Conflict of interest

The authors declare that there is no conflict of interest.

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