ERECTILE DYSFUNCTION

Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction—12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study

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ABSTRACT

Introduction: Short-term data on the effect of low-intensity extracorporeal shockwave therapy (Li-ESWT) on erectile dysfunction (ED) have been inconsistent. The suggested mechanisms of action of Li-ESWT on ED include stimulation of cell proliferation, tissue regeneration, and angiogenesis, which can be processes with a long generation time. Therefore, long-term data on the effect of Li-ESWT on ED are strongly warranted.

Aim: To assess the outcome at 6 and 12 months of linear Li-ESWT on ED from a previously published randomized, double-blinded, sham-controlled trial.

Methods: Subjects with ED (N = 126) who scored lower than 25 points in the erectile function domain of the International Index of Erectile Function (IIEF-EF) were eligible for the study. They were allocated to 1 of 2 groups: 5 weekly sessions of sham treatment (group A) or linear Li-ESWT (group B). After a 4-week break, the 2 groups received active treatment once a week for 5 weeks. At baseline and 6 and 12 months, subjects were evaluated by the IIEF-EF, the Erectile Hardness Scale (EHS), and the Sexual Quality of Life in Men.

Main Outcome Measures: The primary outcome measure was an increase of at least 5 points in the IIEF-EF (ΔIIEF-EF score). The secondary outcome measure was an increase in the EHS score to at least 3 in men with a score no higher than 2 at baseline. Data were analyzed by linear and logistic regressions.

Results: Linear regression of the ΔIIEF-EF score from baseline to 12 months included 95 patients (dropout rate = 25%). Adjusted for the IIEF-EF score at baseline, the difference between groups B and A was −1.30 (95% CI = −4.37 to 1.77, $P = .4$). The success rate based on the main outcome parameter (ΔIIEF-EF score ≥ 5) was 54% in group A vs 47% in group B (odds ratio = 0.67, $P = .28$). Improvement based on changes in the EHS score in groups A and B was 34% and 24%, respectively (odds ratio = 0.47, $P = .82$).

Conclusion: Exposure to 2 cycles of linear Li-ESWT for ED is not superior to 1 cycle at 6- and 12-month follow-ups. **Fojecki GL, Tiessen S, Osther PJS. Effect of Linear Low-Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction—12-Month Follow-Up of a Randomized, Double-Blinded, Sham-Controlled Study. Sex Med 2018;6:1−7.**

Key Words: Erectile Dysfunction; Linear Low-Intensity Extracorporeal Shockwave Therapy

INTRODUCTION

Restoration of natural erection is the ultimate goal of erectile dysfunction (ED) therapy.[1] The introduction of phosphodiesterase type 5 inhibitors (PDE5is) in the late 1990s completely changed the treatment scenario of ED; however, this treatment modality does not represent a cure. Furthermore, most oral medications require planning of sexual intercourse and are associated with, for example, headache, dizziness, or decrease in blood pressure, which can have serious consequences, especially in combination with nitrate preparations.[2,3]

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Penile low-intensity extracorporeal shockwave therapy (Li-ESWT) was previously reported to be capable of curing ED.[4,5] The underlying mechanisms of action remain elusive. Potential beneficial effects related to ED include stimulation of cell proliferation, tissue regeneration, and angiogenesis.[5] In a diabetic rat model, Li-ESWT was shown to promote regeneration of neuronal nitric oxide synthase–positive nerves, endothelium, and smooth muscle cells.[6] The effect seemed to be mediated by the recruitment of endogenous mesenchymal stem cells.[6] In addition, Li-ESWT showed potential in promoting angiogenesis in a pelvic neurovascular injury rat model.[7]

Human clinical trials of Li-ESWT have produced inconsistent results.[8–16] A recent systematic review and meta-analysis concluded that Li-ESWT might be especially suitable for men with mild ED[5]; yet 1 of the included trials only implicated a potential value for severe ED.[11] In addition, in several of the trials, an inconsistency was reported of ED outcome measures after Li-ESWT—International Index of Erectile Function (IIEF) vs Erectile Hardness Scale (EHS)—which are difficult to explain.[17] One reason for the conflicting results might be that the potential of the Li-ESWT–induced tissue regeneration and angiogenesis, which are inherently slow biological processes, might not have reached its maximum at time of analysis. Thus, the effect of nerve regeneration and angiogenesis on ED might have considerable interindividual variance, and therefore long-term data on the effect of Li-ESWT on ED could better elucidate statistical intervariance.[4,5,17]

In this article, we report on outcomes at 6- and 12-month follow-up from a previously published randomized, sham-controlled clinical trial on linear Li-ESWT (LLi-ESWT) for ED.[15]

The objective of the study was to evaluate the effects of LLi-ESWT on ED assessed by the IIEF-EF, EHS, and Sexual Quality of Life in Men (SQoL-M) questionnaires.

The hypothesis of the study was that LLi-ESWT would improve erectile function at 6 and 12 months, possibly through regenerative processes and angiogenesis.

METHODS

Details of the trial (NCT02063061), in which short-term data were reported, were previously published.[15] Participants underwent a standard assessment that included medical history, physical examination, and blood testing. Subjects with vasculogenic ED were selected based on inclusion and exclusion criteria (Table 1). Use of any erectogenic therapy was restricted during treatment and short-term follow-up. Furthermore, in subjects previously treated for ED, a 4-week washout period was implemented.

The study was carried out from February through August 2014 at the Department of Urology at the Hospital of Southern Jutland (Sønderborg, Denmark). This department offers primary urologic care to almost 250,000 inhabitants within a 100-km range.

Table 1. Inclusion and exclusion criteria

Inclusions	Age > 40 y
	Complaining of ED > 6 mo
	In stable relationship (>3 mo)
Exclusions	Surgery or radiotherapy of pelvic region
	Treatment with anticoagulants (except acetylsalicylic acid 75 mg)
	Treatment with antiandrogens
	Anatomic penile deformations or penile prosthesis
	Total testosterone level < 8 nmol/dl
	Serious heart or lung disease
	Psychiatric or neurologic disorder
	Pregnant partner
	IIEF-EF score ≥ 25

ED = erectile dysfunction; IIEF-EF = International Index for Erectile Function erectile function domain.

The research secretary generated a random list (www.randomisation.org) with a 1:1 ratio. 126 subjects were allocated to group A or B. The manufacturer of the ESWT device (Richard Wolf GmbH, Knittlingen, Germany) provided 3 identically looking gel pads that were specially designed for this study. In the 1st phase of treatment, a non-penetrable active gel pad was used. Pads were marked A or B, which corresponded to the sham or active group. In the 2nd phase of the trial, all patients received LLi-ESWT using another active gel pad. It had an outer design identical to those used during the 1st phase, allowing for concealed group allocation during the entire study period for investigator and patients. Participants received 5 weekly treatment sessions of LLi-ESWT or sham. After a 4-week break, the 2 groups received LLi-ESWT. We imitated the crossover design from pharmacologic studies. We chose to treat all subjects in the 2nd phase because we expected that treatment would have a prolonged effect. A summary of the study is presented in Figure 1.

The primary outcome measure was the change in IIEF-EF score from baseline to after 6 or 12 months (ΔIIEF-EF). To enable comparison of our findings with results of other trials,[11,12,16] changes in IIEF-EF score of at least 5 points were considered clinically relevant. Secondarily, we looked for changes in the EHS score in which an increase to at least 3 indicated improvement. Changes in SQoL-M score from baseline to final follow-up assessment also were recorded. Use of additional pharmacologic treatment for ED was controlled using a national prescription database, which is an online platform that enables

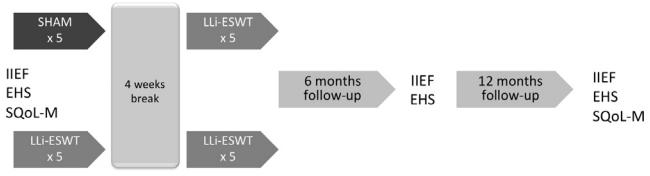

Figure 1. Study design. EHS = Erectile Hardness Scale; IIEF = International Index for Erectile Function; LLi-ESWT = linear low-energy extracorporeal shockwave therapy; SQoL-M = Sexual Quality of Life for Man.

physicians to prescribe medicine and monitor whether patients picked up potency enhancers from the pharmacy.

Treatment sessions consisted of 600 shockwave (SW) pulses with an energy flux density (EFD) of 0.09 mJ/mm^2 and a frequency of 5 Hz delivered within 15 minutes. SWs were given in 3 areas: 300 impulses were administered to the corpora cavernosa in the upright position and 150 impulses were administered to each penile crus in the lithotomy position. The ESWT device was equipped with a piezoelectric linear therapy source (FBL10; Richard Wolf GmbH). Penetration depth in this device is adjusted by applying different gel pads. In our study we used a 0-mm gel pad that allowed treatment of an organ area 1 cm deep and 5 cm wide. The number of impulses used was chosen based on a previous trial reporting positive outcomes after applying focused Li-ESWT, taking into consideration that a linear probe delivers SWs to a wider area of the penis.[9]

Outcomes were assessed using questionnaires (IIEF-EF, EHS, and SQoL-M) at baseline and at 6 and 12 months. Before the 1st treatment session, subjects completed questionnaires on a tablet in a separate room and the research nurse assisted on request. During follow-up, patients received an e-mail with a link that allowed them to submit questionnaires from their own electronic devices at home. All questionnaires had an identical form and layout. Answers were collected on a server (www.surveyexact.dk). Subjects who did not have access to a computer (n = 21) received questionnaires sent by mail with a return envelope. The investigator with the assistance of a secretary transferred those results to the server.

The project was registered at www.clinicaltrials.gov (NCT02063061). The study was approved by the regional ethics committee (ID-20120028), the Danish Ministry of Health (2013073909; CIV-13-07-011546), and the Regional Data Protection Agency. The Good Clinical Practice unit at the University of Southern Denmark monitored the complete research process. The investigator acquired written informed consent before the study.

Statistics Including Power of Study

We included 63 patients in each group, which was required to detect a minimum 5-point change in IIEF-EF score as the primary end point. We assumed a type 1 error of 5%, power of 80%, and common SD of 9.3. We expected 10% dropouts. Outcome measurements were summarized at baseline and 6 months and 12 months after completing the treatment protocol. We present our results as the number of subjects, means, SDs, and 95% CIs. The change from baseline to 12 months was compared between groups using linear regression adjusting for baseline measurements. Adherence to the normality assumption was checked by visual inspection of QQ plots. The change from baseline over time was analyzed by a mixed-effects linear regression with random effects given by the patients and interaction with time. A P value less than 0.05 was considered significant. Statistical analysis was performed with STATA 14 (StataCorp, College Station, TX, USA).

RESULTS

From February through May 2014, we screened 184 patients. 126 participants were found eligible for the study and randomized in 2 groups at the ratio of 1:1. Baseline characteristics are presented in Table 2.

43 subjects (68%) from group A (sham; LLI-ESWT 5 times) and 52 (82%) from group B (LLI-ESWT 10 times) completed the questionnaires 6 and 12 months after treatment. Patients who were found ineligible after randomization (IIEF-EF score > 25, n = 4), those who dropped out during treatment phase (n = 4), and those who did not return questionnaires (n = 23) were excluded from final analysis. A flowchart presenting the inclusion process, according to the Consolidated Standards of Reporting Trials (CONSORT) statement,[18] is shown in Figure 2.

Mean IIEF-EF scores in group B were 10.9 (SD = 7.1) at baseline 13.5 (SD = 9.2) at 6 months, and 12.8 (SD = 9.4) at 12 months. Mean scores in group A were 11.2 (SD = 6.6), 16 (SD = 9.8), and 14.3 (SD = 9.9), respectively. Results at 4-week follow-up after 5 sham treatment sessions (group A) from a previously published article[15] are presented in Figure 3. Linear regression of ΔIIEF-EF score from baseline to 12 months included 95 patients. Adjusting for IIEF-EF score at baseline, the difference between groups B and A was −1.30 (CI = −4.37 to 1.77, P = .4). The success rate based on the main outcome parameter (ΔIIEF-EF ≥ 5) was 54% in group A vs 47% in group B (odds ratio = 0.67, P = .28). The improvement based on changes in EHS score in groups A and B was 34% and 24%, respectively (odds ratio = 0.47, P = .82).

Analysis of IIEF-EF changes over time showed a significant increase from baseline only in group A (P = .001); however, it should be noted that it did not reach the predefined minimal clinically important difference. The difference between groups was not significant (P = .18).

The values of SQoL-M were 37% in group A and 35% in group B at 1-year follow-up. The change from baseline was −6.1% in group A and −6.6% in group B (P = .82).

Adjusting for use of erectogenic drugs did not result in any statistically significant differences between groups. Mean IIEF-EF scores in group A were 11.4 (95% CI = 7.8−15) at baseline, 10.9 (95% CI = 7−14.8) at 6 months, and 9.5 (95% CI = 6−13) at 12 months. Corresponding results in group B were 12.9 (95% CI = 9.5−16.3), 13.1 (95% CI = 8.4−17.8), and 12.6 (95% CI = 8.4−16.8).

Safety

We did not see any serious adverse events of LLi-ESWT during treatment or follow-up. One patient from group A was diagnosed with Peyronie disease (PD) 6 months after the treatment.

Table 2. Patients' basic characteristics

	Population (N = 126)	Group A (n = 43)	Group B (n = 52)
Age (y)	64.9 (10.5)	64.4 (8.3)	66.8 (8.2)
BMI (kgm^2)	27.4 (3.6)	27.6 (3.1)	27.3 (3.8)
Total testosterone (nmol/dL)	14.0 (4.4)	13.1 (4.1)	14.4 (4.9)
Smoking status	22 (17.5%)	12 (27.9%)	6 (10.9%)
Myocardial infarction	15 (11.9%)	6 (13.9%)	5 (11.7%)
Hypercholesterolemia	93/54* (73.8%)	33/20* (76.7%)	35/22* (67.3%)
Peripheral artery disease	11 (8.7%)	2 (4.6%)	8 (15%)
Hypertension	54 (42.8%)	15 (34.9%)	22 (42.3%)
Diabetes	15 (11.9%)	7 (16.3%)	3 (5.8%)
Treatment with PDE5i	—	24 (56%)	30 (58.0%)

BMI = body mass index; PDE5i = phosphodiesterase type 5 inhibitor.
*Diagnosed during screening.

Using a national prescription database to assess the number of patients who were taking medications for ED during follow-up, we found that 24 men (56%) in group A and 30 men (58%) in group B were using a PDE5i and 1 man (2%) in group B was injecting alprostadil.

DISCUSSION

There is an imperative requirement for more long-term data on the effect of Li-ESWT on ED.[4,5,17] In this report we present 6- and 12-month data from a randomized, sham-controlled trial on LLi-ESWT for ED. In line with our previously published short-term results,[15] we did not find a clinically significant effect of LLI-ESWT on ED at our time points. 2 controlled trials on Li-ESWT reporting long-term data on ED have been published.[12,16] Srini et al[16] reported on 12-month follow-up after focused Li-ESWT and found significant increases in the IIEF-EF and EHS domains. However, these results are seriously flawed by a very high dropout rate (58% and 42% in sham and active treated groups, respectively) and therefore should be interpreted with caution. Olsen et al,[12] who initially reported positive short-term results of focused LI-ESWT in the EHS but not in the IIEF-EF domain, found no significant effects at 6 months for either outcome measure. Thus, the overall long-term clinical effects of Li-ESWT, whether focused or linear SW delivery, seem to be doubtful. Indeed, there is reason to doubt the short-term clinical effects of Li-ESWT, because results from randomized trials have been inconsistent, and only 1 of 3 systematic reviews

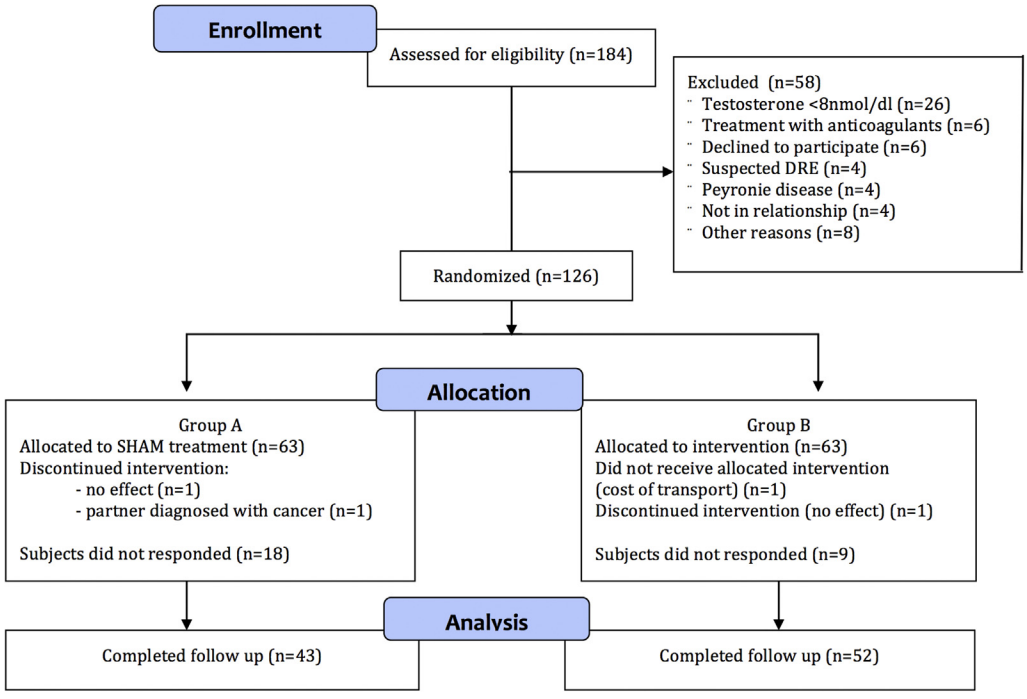

Figure 2. Patient flow diagram. DRE = digital rectal examination; IIEF-EF = International Index for Erectile Function erectile function domain.

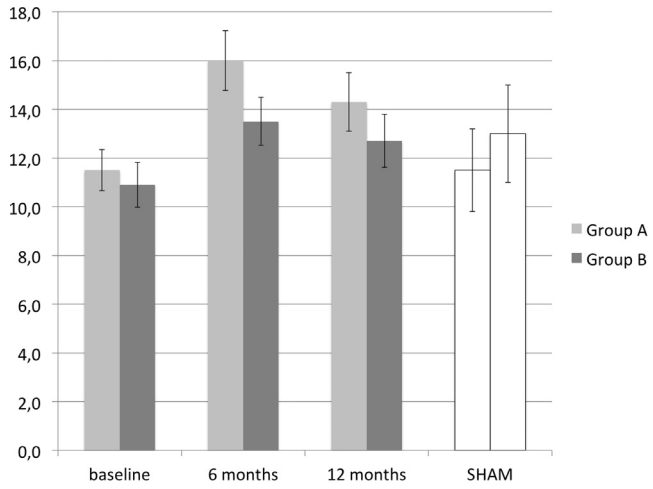

Figure 3. Predicted change of International Index for Erectile Function erectile function domain score (mean and 95% CI) over time. SHAM = effect assessed 4 weeks after 5 simulated treatment sessions.

and meta-analyses on Li-ESWT for ED has documented increases in IIEF-EF[4,5,19] to what is considered the minimal clinically important difference (ΔIIEF-EF score > 4).[20] Whether repeated treatment sessions over a longer period might stimulate cellular and molecular mechanisms, which are believed to be involved in angiogenesis and nerve regeneration translating into significant clinical effects, still needs to be evaluated in controlled trials. Treatment with LLi-ESWT in 2 5-week sessions with a 4-week break (group B) did not result in any positive improvements in IIEF-EF, EHS, or SQoL-M scores. In fact, group A, which received only 5-week treatment, had a better outcome during follow-up, although not reaching the predefined clinically relevant end point (ΔIIEF-EF ≥ 5), suggesting that extending treatment sessions beyond 5 weeks might not achieve superior results.

There could be several reasons for the conflicting results on the effect of Li-ESWT in the literature. Among these are differences in SW technology (piezoelectric, electromagnetic, electrohydraulic), differences in SW delivery (focused, linear), and differences in number of SWs used, which potentially confuse comparison of studies and thus lower the validity of meta-analyses. In our study the number of SWs delivered with the linear probe was calculated based on data from a previous trial using focused ESWT[9] with an identical EFD (0.09 mJ/mm^2).

There are several reports of positive outcomes of LLi-ESWT for ED.[14,21–23] 3 trials applied an electromagnetic device (Renova, Direx Systems GmbH, Wiesbaden, Germany).[21–23] Bechara et al[21] and Reisman et al[22] treated their patients with 3,600 SWs and an EFD of 0.09 mJ/mm^2 in 4 weeks, and Pelayo-Nieto et al[23] applied the same energy level but their treatment protocol consisted of 4 treatments of 5,000 SWs. Motil and Sramkova[14] tested the same piezoelectric therapy source used in the present study. Their treatment protocol involved 4 weekly sessions of 4,000 SWs, an EFD of 0.16 mJ/mm^2, and a penetration depth of 10 to 15 mm. Positive clinical effects were reported in all cited trials; however, only the study of Bechara et al[21] was designed as a randomized controlled trial and the others were open-label trials.[14,22,23] Considering those encouraging outcomes and absence of serious adverse effects, it seems safe to proceed with planning LLi-ESWT trials using a larger number of SWs. The advantage of linear ESWT is that usage of the linear probe delivers SWs to a wider area of the corpora cavernosa, thus limiting movements of the probe during treatment compared with focused ESWT, which could decrease user dependency.[14] However, before clinical trials on ESWT in ED are performed, dose-finding studies defining the right protocol settings for the specific device tested should be mandatory, which to a large extent has been neglected in previous trials including ours. Recommending Li-ESWT as a treatment option for ED needs to be properly scientifically evaluated, because offering the treatment without evidence carries serious ethical issues.[24]

In general, health care professionals should be aware that ED might be an indicator of endothelial dysfunction that precedes vascular events.[25] Therefore, when applicable, lifestyle changes should always be recommended to decrease vascular risk factors, which have been shown to improve IIEF-EF score.[26,27]

Limitations

We estimated treatment dose based on the trial of Vardi et al,[9] in which a focused transducer was used. In our trial we used a linear probe, and the lack of a dose-finding study can be considered a limitation of our study. Furthermore, owing to our study design, we could assess only short-term effects of sham treatment, because all participants received active treatment in the 2nd phase. Results obtained 4 weeks after 5 simulated treatment sessions (sham) served as a control.

In our short-term data we had a very low dropout rate (3%).[15] In the present report, 25% of patients were lost to follow-up, which might have introduced selection bias.[28] The difference in dropout rate between groups A (32%) and B (17%) might explain the better outcome in patients who received only 5 treatment sessions (group A), because an uneven dropout can introduce potential bias favoring positive outcomes.[29] Furthermore, a larger proportion of men in group B complained of peripheral artery disease, which could be indicative of more severe endothelial dysfunction, and thus they would be expected to have a poorer response. Differences in tobacco usage and prevalence of diabetes between the 2 groups also could have affected the outcome.

We did not apply objective measures for diagnosis of ED etiology. Usage of duplex ultrasonography to confirm vascular insufficiency for patient selection might have resulted in a different outcome.

The gel pad applied in our study was originally developed for treatment of skin wounds. In this configuration, some of the

acoustic energy is restricted to the transducer and thus might not be effectively transmitted to the site of need. Different gel pad designs might be more effective, and in future studies a greater penetration depth of SWs could be a target of interest.

Results of previous trials[9,12,14] suggested that PDE5i responders showed significantly improved erectile function. Our trial was not specifically powered to make distinctions between PDE5i responders and non-responders.

Safety

There has been concern that repeated Li-ESWT treatments can result in fibrosis of the corpora cavernosa and eventually the development of PD.[30] In our series 1 patient developed PD with classic plaques and 30° angulation 6 months after treatment. The patient was in group A, meaning that he received ESWT only during the 2nd round of treatment. Men in group B, who received 2 rounds of ESWT, had no long-term complaints, suggesting that the case of PD was coincidental and not related to the SW effects.

Strengths

Using a national prescription database, we could reliably identify patients who were using pharmacologic treatment for ED during the follow-up period. The proportion of men using medication for ED during follow-up was comparable between groups. During the complete trial, data collection and management were monitored by an independent Good Clinical Practice unit, which also could be considered a strength of the study.

CONCLUSION

This study showed that 2 cycles of LLi-ESWT for ED (10 treatment sessions) were not superior to 1 cycle (5 sessions) at 6- and 12-month follow-up. Targets for future Li-ESWT research could be increasing the penetration depth and the number of SWs. Because the effect of Li-ESWT on ED is questionable, treatment of patients with ED with this therapeutic modality preferably should be confined to controlled clinical trials.

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